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A Manual of
PHARMACOLOGY
and Its Applications to
THERAPEUTICS AND TOXICOLOGY

By
TORALD SOLLMANN, M.D.
Professor Emeritus of Pharmacology and Materia Medica,
School of Medicine, Western Reserve University, Cleveland

SEVENTH EDITION

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PREFACE TO THE SEVENTH EDITION

This Manual of Pharmacology again aims to furnish a rather comprehensive outline of current knowledge and conceptions of drug actions, especially from the point of view of their practical importance in therapeutics and toxicology. The last few years have brought extensive developments in this field, partly foreshadowed in the preceding period, but greatly accelerated, intensified and focused by the demands of war. These have led to some profound changes in emphasis and attitude. The most impressive discoveries perhaps are in the field of the highly potent anti-infective agents which check the multiplication of parasites within the body by interfering with essential features of their nutritional metabolism. This has a vast practical importance as a new concept of "chemotherapy," because it utilizes actions specifically harmful to the invader, but not to the host; and it also promises a better insight into the nature of pharmacological actions, or at least into the metabolic phases of these, which have long baffled inquiry.

The entirely new "antibiotic" agents are not the only ones that have profited by intensified research activity. There have also been important advances in other selective anti-infective agents, the sulfonamides, the antimalarial drugs, the antimonial drugs, the insecticides and rodenticides, the auxins and weed killers. Vitamins and hormones have become more important as information has increased. The antithyroid drugs, anticonvulsants, antihistamine agents, anticholine-acetylases, folic acid, standardized curare, reliable digitoxin, "nitrogen mustards," and BAL have opened new fields of knowledge and use.

Drug therapy seems to stand in the doorway of a new era, or rather has already entered, and is perhaps tempted to close the door upon the old. However, the importance of many of the older drugs has not diminished. Anesthesia, systemic and local, is as vital as ever; so are analgetics and digitalis, and many others. But their use has been modified: Medication has become more "heroic." The prime essential of therapy has gradually changed from the aim of "do no harm" to that of "do some good" even if this involves a risk, provided that the probable benefit is materially greater than the probable injury. It is justified only if the risk is fully understood. This requires a thorough knowledge of the actions of these drugs, with all the light that pharmacology can throw upon them. It requires also a broad background of the actions of drugs in general. However, a number of the older drugs have declined in importance, some to the point of insignificance. Others are again on trial, and the information about them should be available without too much difficulty.

The revision of this book has aimed to strike a reasonable balance by subordinating what appears of questionable value, and eliminating what no longer has real importance or interest; stressing critical observations and subordinating speculations that lack factual foundation. The statements are supplemented by references to the authors where more information may be found if desired. The citations are primarily for this purpose rather than for assigning credit. The bibliography in the back of the volume has again been restricted to the last twenty years, or, rather, from January 1st, 1926; earlier authors may be generally located through the later papers, or through the Index of the Surgeon General's Library, or in the earlier editions of this book.

As in the former editions, the text in ordinary type presents the material that *all* students should aim to know; small type contains the data that would be consulted only as special occasion arises. The new arrangement in two columns should facilitate the search for information.

I would again thank the W. B. Saunders Company for careful composition and production of the book.

TORALD SOLLMANN

Cleveland, Ohio

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A Manual of
PHARMACOLOGY

PHARMACOGNOSY

Pharmacognosy (the knowledge of drugs) deals with the origin, anatomical structure and chemical composition of crude drugs. The obsolescent title "Materia Medica" includes also the actions and uses, now generally called "Pharmacology."

Drugs are derived from the three natural kingdoms, the animal, vegetable and mineral and from the "fourth estate" of synthetic chemistry. Natural plants furnish the greatest variety of chemical substances and, therefore, the greatest number of drugs.

Vegetable Drugs.—The active principles are often diffused throughout the plant, but they are generally more abundant in the part which is used as medicine. The following are technical names of the more important parts, with some characteristic examples:

Root (*Radix*): The underground part of the plant, which is generally devoid of chlorophyl (green coloring matter) and does not produce leaves (Dandelion, Belladonna, Ipecac, Rhubarb). **Tuberous Roots:** Roots swollen with accumulation of reserve food material (Sweet Potato, Aconite, Jalap). They are often called *tubers*; but true tubers (Potato) are similar formations on rhizomes. **Corm:** A thickened underground stem (Colchicum). **Bulb:** Very fleshy, closely crowded leaves, enfolding the underground base of the stem (Onion, Squill). **Rhizome:** Underground stems which bear leaves (Podophyllum, Hydrastis, Ginger, Aspidium). **Wood** (*Lignum*): The wood of trees, in fragments, chips or coarse powder (Quassia, Hematoxylon, Sandalwood). **Bark** (*Cortex*): The outer layer of the stem (Cinchona, Cascara, Wild Cherry) or of the root (Sassafras, Cotton-root). Sometimes only the inner bark is collected (Ceylon Cinnamon, Elm). **Leaves** (*Folia*): Digitalis, Uva Ursi, Belladonna, Senna. **Herb** (*Herba or Species*): The smaller leafy and flowering or fruiting stems (Peppermint, Cannabis Indica, Savin). **Flowers** (*Flores*): Chamomile, Arnica. Unexpanded flowers are: Cloves, Santonica. **Fruit** (*Fructus*): The ripened ovary, with any persistent parts of the flower, containing the seeds (Pepper, Hops, Colocynth, Anise). **Seed** (*Semen*): The essential part of the fruit (Nux Vomica, Strophanthus, Physostigma, Mustard, Linseed).

The **microscopic structure of plants** differs from the animal cells, especially by the thick cell walls, and by the frequent presence of protoplasmic enclosures, starch, fats, calcium oxalate, protein crystals, etc. The cell walls are chiefly responsible for the shape and physical properties of the cell. They consist primarily of cellulose, variously modified by certain allied substances (lignin in wood, suberin in cork). These are insoluble in ordinary solvents and in the alimentary canal of man. The processes of pharmacy consist largely in separating the active constituents from this inactive material.

IMPORTANT PLANT CONSTITUENTS

These belong to the chemical groups of proteins, fats, carbohydrates, tannins, resins, alkaloids, glucosides, acids, terpenes and inorganic salts. Plants of the same family generally produce substances with similar chemical structure and actions (Jussieu), but there are many exceptions, and indeed a single plant may form substances of various actions.

Cellulose is found in the cell walls. It exists in almost pure form in cotton. It is an isomer of starch. It is insoluble in all ordinary solvents, and is not affected by boiling water. It dissolves without change in Schweitzer's reagent (ammoniated solution of copper sulphate). In older cells it is often modified by the introduction of allied molecules: *wood* (lignin) or *cork* (suberin). Cork is very resistant to reagents and impermeable to water, and hence protects the plant against evaporation and chemic injury. Cellulose may undergo a retrograde metamorphosis into gum or pectin.

Starch $(C_6H_{10}O_5)_n$ is produced as one of the first stages in the assimilation of CO_2. The starch molecule probably consists of a long chain of monosaccharide molecules linked by primary bonds (Staudinger and Hausmann; W. Z. Hassid, 1943). It has two chemically distinct carbohydrate components, amylose and amylopectin (W. Z. Hassid, 1945). It occurs in the form of granules, usually showing a laminated structure around a center (hilum). The character of this lamination, as well as the average shape and size of the granules, is important in distinguishing between different plants.

Starch can be recognized by the blue color which it gives with iodine. It is insoluble in all ordinary solvents, but swells with boiling water and forms a peculiar colloidal solution (paste), which is precipitated by alcohol. It is hydrolyzed by acids and by diastases, yielding dextrin (which colors red-brown with iodine) and then glucose.

Gums are colloidal carbohydrates, swelling or dissolving in water to viscous adhesive fluids (mucilages or pastes). They are precipitated by alcohol. They are formed in the plant by the transformation of cellulose and cell contents, especially as the result of pathologic processes. They yield glucose when hydrolyzed by acids. *Hemicellulose,* which occurs in seaweed (agar), lichens and fungi, is more difficult to hydrolyze. *Pectins* are related substances, occurring in fruits and causing the boiled fruits to set into jelly. Gums and pectins do not color with iodine; they reduce copper only after inversion.

Sugars are carbohydrates, of more or less sweet taste, generally freely soluble in water, sparingly soluble in alcohol, insoluble in fat solvents. Some reduce copper directly, others only after hydrolysis. They contain an asymmetric carbon, and therefore rotate polarized light. The more important types are: *Glucose* (*Dextrose*) and *Levulose,* $C_6H_{12}O_6$; *Maltose* and *Saccharose,* $C_{12}H_{22}O_{11}$; and *Mannite,* $C_6H_{14}O_6$.

Glycosides are ester-like combinations of sugars with various other substances (genins), frequently with phenols. Acids or appropriate enzymes hydrolyze them into sugar and the other substances. Many do not contain nitrogen. Most glycosides are neutral or weakly acid; a few are alkaloidal. They are widely distributed in plants, and include the digitalis constituents, saponins, tannins, etc. Their pharmacologic actions are generally inherent in the genin, the sugars modifying the penetration, persistence and reactivity.

Saponins are also widely distributed. They are so called because they foam like soap, emulsify oils and lake red blood corpuscles. They are neutral, non-nitrogenous substances related to bile acids in structure and action. Some are glucosides. Those which are markedly toxic are called *sapotoxins,* but they are generally not very poisonous by mouth, because they are poorly absorbed.

Tannins are a group of phenol derivatives, distinguished by giving a bluish or greenish color with ferric salts. The greater number also form insoluble compounds with other metallic salts, with alkaloids, proteins, etc. This precipitation leads to astringent action. Tannins occur in many plants, especially in the leaves and bark, and in pathologic formations (nutgalls). They are non-nitrogenous; some are glucosides. They are soluble in water and in alcohol; but since they form insoluble compounds with many substances, they often occur in plants in granular form.

Tannins are easily decomposed into resin-like substances called *phlobaphenes.* These exist naturally in plants, but are usually formed as decomposition products in extractions. They are dark-colored, soluble in alcohol and in alkaline liquids, insoluble in water. Tannins and phlobaphenes, as well as most other plant constituents, are easily converted into a group of substances called *humins.* These do not exist in living tissues, and arise on the death of the cells, by the action of air and moisture. They cause the brown color which plants assume on drying; they are also present in the brown bark. Tannins, phlobaphenes and humins form a series without sharp demarcation. They are rather resistant to the action of bacteria and in this way protect plants against putrefaction.

Alkaloids comprise many of the most active and important plant constituents. They may be defined as natural nitrogenous organic bases (generally tertiary amines); *i. e.,* they are organic substances, containing nitrogen, of basic character, combining with acids without the elimination of hydrogen, forming well-defined and usually crystalline salts. The salts with halogens are called hydrochlorides, hydrobromides, etc. (not chlorides, etc.). The names of alkaloids are spelled with a final *e,* to distinguish them from neutral principles (thus morph*ine,* an alkaloid; sali*cin,* a glucoside).

The *discovery of the alkaloids* is an achievement of the 19th century (morphine, by Sertuerner, 1805 to 1817; strychnine, 1818; quinine and caffeine, 1820; nicotine, 1829; atropine, 1833). Alkaloids are of common *occurrence* in the higher plants, the same plant usually containing several alkaloids, which are often formed from one another. They may be found in all parts of the plants, but sometimes they are strictly localized in certain portions. They are probably metabolic waste products (F. A. Henry, 1927). The alkaloidal content varies according to the climate, culture and other conditions. Individual plants also show considerable variations. They can be improved by selected breeding (Sievers, 1913, 1916). Alkaloids are also formed by bacteria ("ptomaines") and molds. The active amines of animals, such as epinephrine, may be considered as alkaloids.

Properties of Alkaloids.—Most alkaloids have a bitter taste, alkalinity to litmus, nitrogen reaction; generally profound physiologic action, without postmortem lesions; some alkaloids contain oxygen; others do not. Those containing oxygen are solid and comparatively nonvolatile; those free from oxygen (nicotine and coniine) are liquid and volatile. Free alkaloids are *soluble* in ether, chloroform, and oils, much less soluble in alcohol, and comparatively insoluble in water. Alkaloidal salts have the opposite solubility: They are soluble in water and alcohol, insoluble in chloroform and ether. This reversal of solubility is used to isolate alkaloids from crude drugs and mixtures. Alkaloidal salts are *precipitated* by iodine, mercuric-potassic iodide (Mayer's reagent); phospho-molybdic acid; picric acid; gold chloride, platinic chloride, etc.; some precipitate mercuric chloride, potassium bichromate, tannin, etc. Many alkaloids give characteristic *colors* with concentrated acids, with or without the addition of oxidizing or reducing agents. The chemical *structure* of many alkaloids is well understood; others are still obscure. The greater number are fairly complex derivatives of *pyridine* (coniine, nicotine); *pyrrolidine* (cocaine, atropine); *quinoline* (quinine, cinchonine); *isoquinoline* (hydrastine, narcotine, cotarnine, berberine); *morpholine* or *phenanthrene* (morphine, codeine, thebaine).

Neutral or bitter principles are a heterogeneous group of substances which have not been assigned to other classes. They usually have a bitter or sharp taste, and are generally crystalline and non-nitrogenous. A number are *lactones*.

Resins are also a heterogeneous group, including solid, nonvolatile, amorphous substances of obscure composition, commonly non-nitrogenous. Their distinguishing character is insolubility in water and solubility in alcohol, most fat solvents (except petroleum ether) and strong alkalis. The resins are often contained in special vessels, from which they exude after incising the plant. When the resins occur mixed with essential oils, they are *natural oleoresins;* when mixed with gums, *gum-resins.* If they contain aromatic acids (cinnamomic, benzoic, etc.) or essential oils, they are called *balsams. Resinoids* are artificially isolated principles soluble in alcohol and insoluble in water. They are generally mixtures, often containing true resins.

Volatile oils (essential oils) are odorous principles, of the physical characters of fatty oils, except that they are volatile and soluble in alcohol. Chemically, they are mixtures of esters, aldehydes, alcohols, ketones and especially terpenes (Kremers, 1898). The constituents may separate on cooling, the liquid part being called *eleoptene,* the solid *stearoptene. Camphors* are analogous substances, but solid at ordinary temperature. *Rubber* (caoutchouc and gutta-percha) is related to the terpenes. Plants also contain many other alcohols, aldehydes, organic acids, aromatic derivatives, etc.

Fats and fixed oils (esters of fatty acids and glycerin) are abundant, especially in seeds, occurring within the cells as drops or crystals. The fats are greasy liquids or soft solids; when heated, they undergo decomposition, denoted by acrid acroleine vapors. They are insoluble in water or glycerin, sparingly soluble in alcohol, and freely soluble in ether, chloroform, benzine (petroleum ether), carbon disulfide, turpentine, etc. (*fat solvents*).

Waxes are more solid substances with the solubility characters of fats. They are esters of fatty acids with alcohols other than glycerin.

Proteins are represented in all vegetable cells, but are especially abundant in seeds, sometimes as crystals (aleuron). Several classes of the proteins are peculiar to plants.

Chlorophyl, the green pigment of plants, is insoluble in water, soluble in alcohol and fat solvents. It is allied to blood pigment, but contains magnesium instead of iron. It is readily changed and discolored by reagents.

The chlorophyl occurs in the cells as granules (chloroplasts), made up of a colorless, spongy, protein groundwork, containing in its meshes the chlorophyl pigment, which consists of a mixture of green and yellow colors (chlorophyl and xanthophyl). Chlorophyl is found mainly in the higher plants, and serves in the presence of light to assimilate CO_2 and to form starch. During drying, especially if this occurs slowly, the pigment is acted on by acids, etc., developed under these conditions, and undergoes various changes, usually becoming brown.

Other Pigments.—Plants are rich in colors belonging to various chemic groups, often unidentified. Many alter with changes of reaction. The brown coloring matter of barks, etc., is allied to the tannins and phlobaphenes.

Enzymes of many kinds occur in different plants, a few being used in medicine.

Extractive matter is a term applied to the mixture of unidentified organic constituents which remains as a smeary mass after evaporating extracts from which the important constituents have been removed.

Mineral salts are fairly abundant in plants, constituting the ash which remains on incineration. Ca and K are especially important.

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PHARMACEUTIC STANDARDS

Pharmacy deals with the preparation and compounding of drugs for the purpose of administration. It has for its *objects* the separation of the active principles of drugs, their combination, and their presentation in acceptable form.

Official Drugs.—Civilized countries have standards established by law, to which drugs and preparations in the shops must conform. The book in which these standards are published is usually called the *Pharmacopeia.* Preparations listed in these official books are termed "official." A pharmacopeia, therefore, is an official book of standards for official drugs. The "*United States Pharmacopoeia*" and the "*National Formulary*" are now revised every five years. The current editions are designated as "*U.S.P. XIII*" and as "*N.F. VIII.*" The standards of the U.S.P. apply solely to articles intended for medicinal use.

International Uniformity.—The first effective step in this direction was taken by the Brussels Conference of 1906, the "International Conference for the Unification of the Formulas for Potent Medicines." This conference drew up a list of the potent drugs for which uniformity was most important, and established standards of strength for them and their preparations. These have been adopted essentially by most of the civilized nations. The standards of the Brussels Conference of 1925 are designated as "P.I." (Protocol International) by the U.S.P.

Scope of the Pharmacopeias.—These usually aim to include only "standard drugs," *i. e.,* those of established value. There is a healthy tendency to restrict the admission of complex mixtures.

Galenic Preparations.—"Galenicals" are, strictly speaking, medicines prepared after the formulas of Galen. The term is now used to designate preparations containing one or several organic ingredients, as contrasted with pure chemic substances.

Proprietary Drugs are protected by monopoly, generally by patent or trademark, or by secrecy. Those concerning which information is freely available are generally official in the U.S.P. if their value has been sufficiently established, or in "N.N.R." (see below) provided that they are marketed under proper conditions.

"**Patent medicines**" is a term applied to proprietary drugs that are advertised, directly or indirectly, to the laity. They are not usually patented, as the name would imply; most manufacturers prefer to rely upon secrecy to impose on the public. The medical profession is generally opposed to patent medicines as a class, and to lay advertising in particular. "The impossibility of controlling the irresponsible claims which are usually made in advertisements to the public, the well-known dangers of suggesting by descriptions of symptoms to the minds of the people that they are suffering from the many diseases described, the dangers of the unconscious and innocent formation of a drug habit, and the evils of harmful self-medication, including the dangers of the spread of many infectious and contagious diseases when hidden from the physician, and similar well-known considerations, are the reasons for discouraging, in the interest, and for the safety, of the public, this reprehensible form of exploitation" (N.N.R.).

The Federal Food and Drug Act, which went into full effect in 1940, greatly improved the situation by giving to the Food and Drug Administration broad powers to enforce the pure food and drug laws, and to establish standards for drugs not in the U.S.P. or N.F. No new drug may be introduced until its safety has been demonstrated to the satisfaction of the Administration; and if it is not sufficiently safe it may not be sold directly to the laity. Labels must bear adequate directions for use and warnings against abuse. The active ingredients must be so designated. The Food and Drug Act, however, does not pass on the value of drugs except that they must not be "*misbranded*" by making false claims on the package. Other advertising is under the jurisdiction of the Interstate Commerce Commission.

"The United States Pharmacopoeia" was first published in 1820. It is revised at five year intervals by a Pharmacopoeial Revision Committee, appointed by the United States Pharmacopoeial Convention, which consists of delegates from pharmaceutical and medical organizations. The current committee of revision consists of fifty members, headed by an executive committee. The "U.S.P. Vitamin Advisory Board," organized at the time of the eleventh revision, establishes standards for vitamin preparations, while a similar board, the "U.S.P. Anti-Anemia Preparations Advisory Board," organized at the same time, establishes standards for anti-anemia preparations. The standards of the Permanent Commission on Biological Standardization of the League of Nations Health Organization and the National Institute for Medical Research, of London, England, for vitamins and for digitalis have been the standards of comparison for similar "U.S.P. Reference Standards" now distributed in the United States by the U.S.P. Board of Trustees. Other "U.S.P. Reference Standards" are a "Reference Pepsin" and a "Reference Ergotoxine Ethanesulfonate." The Pharmacopoeial Board also distributes other International Biological Standards as a representative of the League of Nations Committee. **"The British Pharmacopoeia,"** the B.P., published by the General Medical Council, resembles the U.S.P. in scope and arrangement.

"New and Nonofficial Remedies" (N.N.R.) contains descriptions of the characters, actions and uses of those proprietary drugs that are marketed in a proper manner. It is issued by the American Medical Association and revised annually by its Council on Pharmacy and Chemistry. **"National Formulary"** (N.F.) is a collection of formulas for less important preparations, issued by the American Pharmaceutical Association. It is also a legal standard. **"Dispensatories"** are commentaries which enlarge and explain the official texts, and generally also describe unofficial preparations. The U.S. Dispensatory is principally used in the United States. The British Pharmaceutical Codex (B.P.C.) is a similar work. **"Useful Drugs"** is a small manual issued by the American Medical Association which contains only the most useful drugs with such information as is of especial interest to physicians. **"Physicians' Epitome of U.S.P. and N.F.,"** another A.M.A. publication, gives brief abstracts of all U.S.P. and N.F. preparations.

PHARMACEUTIC METHODS

These are adapted to the physical and chemic nature of the crude drug and to the character of the desired product. They may be roughly classified into *general methods* used in the making of many different preparations, and *special methods* used in a limited number. The methods may be discussed in the order in which they are usually applied to the drug.

PREPARATORY PROCESSES

Desiccation or drying is usually the first operation to which the crude drugs are subjected after their collection. It reduces the bulk, assists preservation and facilitates comminution.

Drying was formerly effected by spreading or hanging the drugs in airy lofts. At present they are usually placed on perforated trays in special drying closets and heated artificially (steam, etc.). They are often cut into smaller pieces before this drying. The degree of heat must not be so high as to injure the sometimes unstable ingredients. The U.S.P. designates 32° to 39° C. as "gentle heat."

Comminution, or reducing of the substance to smaller pieces, is usually done by machinery.

Crude vegetable drugs are first sliced or chopped, often before drying. They are then bruised by pounding in a mortar and finally ground, the finer grades of powders often several times, the grinding surfaces being brought closer together each time. The mills for this purpose employ the same general principles as flouring mills. On the small scale, drug mills, constructed more or less on the principle of the coffee mill, are used for fibrous, and mortar and pestle for friable, drugs. Mortars are made of iron, wedgewood, porcelain, and glass.

Pulverization is comminution to a powder. *Trituration* is a process of rubbing (not pounding) a substance to a powder in a mortar.

Fineness of Powder.—It is often essential to use a powder of a certain degree of fineness, especially for percolation. The powders are therefore sifted, and are classified according to the size of the meshes of the sieve through which they pass, thus: No. 80 = 80 meshes to linear inch, very fine. No. 60 = 60 meshes to linear inch, fine. No. 40 = moderately coarse. No. 20 = coarse. Since the different structures in a crude drug do not powder with equal readiness, it is necessary that the whole of the drug to be powdered should be passed through the sieve.

Levigation is employed to obtain very fine powders of insoluble substances by making them into a thick paste with water, and rubbing this between polished slabs. *Elutriation* is used to separate fine insoluble powders by suspending them in water and decanting.

PROCESSES OF SEPARATION

Three methods are available for the separation of the desired ingredients from inert material: Volatile constituents may be separated by the *application of heat*—distillation and sublimation. If they are not volatile, the separation is usually affected by exposing the drug to the *action of a solvent* in which the desired principles are soluble, and the undesired constituents are insoluble. In some cases mechanical means are sufficient, as in the separation of fixed oils from seeds, etc., by *pressure.*

Desiccation (drying), **torrefaction** (roasting), **carbonization, ignition** drive off some volatile constituent from a solid, the fixed residue being the portion desired.

Evaporation consists in vaporizing the solvent from a solution, the object being the concentration of the dissolved substance.

Sublimation separates a volatile from a nonvolatile solid by heat.

Distillation separates a volatile liquid from a less volatile liquid or solid.

Solution incorporates a solid into a liquid in a state of "molecular subdivision." Applied to crude drugs, it separates the active ingredients from the insoluble inert materials.

Maceration, the simpler process, consists in leaving the solvent in contact with the drug under suitable conditions for a sufficient length of time.

When maceration alone is employed, a given quantity of the drug is put in a suitable vessel with a definite proportion of the solvent (called *menstruum*) and left a certain time, usually a week or two. The liquid is then strained off, the residue (*marc*) is expressed and the mixed extract filtered. Maceration offers the advantages of simplicity and constant results. Its main disadvantages are the required time and the loss of the extract retained in the insoluble residue.

Percolation consists in passing a solvent through a thick layer of the powder to be exhausted. This exposes a large surface of the latter; the nearly saturated solvent flows off and fresh unsaturated portions continuously replace it, insuring very rapid solution. The powder is packed into a tall vessel, with an opening at the bottom, and the solvent trickles through it. The process is usually preceded by a short maceration.

The powder (the fineness of which depends upon the nature of the drug and is directed for each case by the Pharmacopoeia) is moistened in a jar with some of the menstruum. This moistening is for the purpose of swelling the drug, for if this took place in the percolator, the drug would become so firmly impacted that the menstruum could not penetrate through it. The moistened powder is then passed through a coarse sieve and transferred to the prepared percolator, which it should fill about two-thirds. The firmness of the packing is important; if it is not firm enough, the menstruum runs through too rapidly and the percolate will consequently be weak. If too firm, it can not run at all. Drugs in coarse powder should be packed more firmly than fine powders. An alcoholic menstruum requires firmer packing than a watery one. The packing being completed, the menstruum is poured on until it stands an inch or two above the drug; the percolator is then covered and set aside for maceration for a specified time, the tube being raised so that no liquid flows out. When the time of maceration is completed, the tube is lowered, and fixed at such a level that the outflow occurs at the rate of 2 to 15 drops per minute. New menstruum is poured on as the old flows out. A layer of liquid must be maintained above the powder, else cracks may appear and necessitate repacking. *The choice of a menstruum* may be determined by the nature of the constituents, so as to extract all the active ingredients and the minimum of inactive. Alkaloids and resins require strong alcohol; gums, weak alcohol; licorice, alkaline alcohol; sanguinaria and ergot, acidified alcohol; gentian and quassia, water plus alcohol enough to keep.

Pharmaceutic Solvents.—The most useful are the following:

Water or glycerin dissolves salts (including those of alkaloids), sugar, gums, tannin, acids, alkalis, etc. *Dilute acetic acid,* especially for alkaloids. *Alcohol* dissolves alkaloidal salts, neutral principles, resins, volatile oils; precipitates gums and most inorganic salts. Ether, chloroform, acetone dissolve free alkaloids, neutral principles, resins, volatile and fixed oils, and fats. *Petroleum benzene* has the solvent properties of the preceding, except resins. *Aromatic spirits of ammonia* dissolves resins and organic acids.

Expression separates a liquid from a solid by pressure. Its principal employment in pharmacy is for the recovery of tinctures from the "marc," *i. e.,* the liquid retained by the drug residue after maceration and percolation. It is also a process of separating fixed oils. The drug is put in a coarse strong cloth and subjected to pressure in a press.

Straining or **colation** separates coarse solid particles from a liquid by pouring it through a cloth or strainer.

Filtration separates solid particles (fine or coarse) from a liquid by pouring it through a finely porous material, such as filter paper.

Dialysis may be used to separate crystalloids (alkaloids, salts, etc.) from colloids (extractives).

Decolorization may sometimes be accomplished by choosing appropriate solvents; or the solution is filtered through activated charcoal. This may retain some of the active constituents as well as the coloring matter.

Clarification removes suspended solids: when filtration does not suffice, it is accomplished by agitating the mixture with insoluble powders (talcum, phosphate of lime, aluminum hydrate) or by adding egg albumen and boiling; or by centrifugation.

Sterilization, the destruction of bacteria and their spores, employs the various customary methods.

Solutions that are not readily decomposed by heat may be boiled in a current of steam for one-half or, better, one hour. *Solutions that are readily decomposed* by heat are either prepared aseptically or filtered through porcelain. *Emulsions in glycerin or oil* are prepared aseptically, the solvent being first sterilized by heat.

PHARMACEUTIC ASSAYING

Different samples of vegetable drugs may vary widely in active constituents. These variations are especially undesirable when they occur in potent, so-called *"heroic" drugs.* Definite chemic compounds are not subject to this variation, but the removal of the last traces of innocuous impurities may greatly increase their cost without adding to their therapeutic usefulness. The Pharmacopoeia has therefore aimed to furnish quantitative methods of estimation, assays, wherever possible, and to establish practical standards to which medicinal substances must conform. With inorganic drugs, it states the largest permissible quantity of innocuous impurities (usually less than 2 per cent). With crude vegetable drugs, it states the permissible limit of foreign matter and insoluble ash, etc.; and the lowest permissible percentage of active ingredient, wherever practical methods for their determination are available. Assayed galenic preparations are adjusted to contain a definite proportion of active constituents.

The *assay of inorganic drugs* involves the methods of ordinary quantitative analysis, volumetric processes being preferred. Special tests are furnished for determining the permissible limits of accidental *impurities,* and the presence of harmful substances, such as metals. A series of volatile oils are assayed for their *most important ingredient.* Fats and fixed oils are tested for their "iodine absorption" and "saponification values"; resins for the "acid number"; some vegetable products for their ash. These tests serve mainly for identification and the exclusion of wilful adulterations.

Drugs containing aklaloidal principles are assayed by utilizing the method of immiscible solvents. In principle, alkaloids are extracted by chloroform or ether, or a mixture of both, in alkaline reaction. This solution is then shaken in a separator with acidulated water, which converts the alkaloids into salts and dissolves them, leaving the impurities behind. For futher purification, the watery solution is again rendered alkaline and extracted with chloroform or ether. On evaporation, this leaves the fairly pure alkaloid which may be weighed; or titrated, by dissolving it in a known amount of acid, and titrating back with alkali. This estimates the sums of all the alkaloids present in the drug, and suffices when the important one predominates largely over the others. Otherwise the assay must be confined to the particular alkaloid desired. For Opium, advantage is taken of the comparative insolubility of the morphine in ether. In Nux Vomica, the brucine is removed by oxidizing it with nitric acid.

Bio-Assays.—Drugs which depend for their activity on neutral principles are often unsuited to chemic assay, there being no reliable chemic method for estimating the constituents of such important drugs as digitalis, ergot, pituitary extract, etc. These are adjusted by **physiologic standardization,** estimating the strength of a preparation by comparing its effects on animals with those of the *"reference standard"* product, issued by the U.S.P. Revision Committee and approximately identical with the International Standards of the League of Nations Commission. The potency is generally expressed in *"units'* which are similarly identical (except for Tetanus Antitoxin). The more important methods are described in the U.S.P. Bio-assays are more difficult and more variable than the best chemical assays, partly because of the natural variability of living objects, and partly because they are often used for complex drugs. The criteria must be selected so that they reflect the therapeutically important ingredient, although not necessarily the therapeutic action. The variability must be discounted by using a sufficient number of animals and by suitable statistical methods (Burns, 1930). The fundamentals of biological assaying are reviewed by C. I. Bliss and Cattell, 1943. The cost of the animals makes bio-assays relatively expensive.

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CLASSES OF PHARMACEUTIC PREPARATIONS

The Latin titles in the following are given in the singular.

WATERY SOLUTIONS

These include the Waters, Liquors, Mucilages and Syrups. Their advantage is that water is a cheap solvent of wide applicability, itself devoid of any therapeutic property. The greatest drawback lies in the fact that watery solutions of organic substances tend to spoil rapidly by the development of micro-organisms. Solutions of chemic substances are less subject to this change.

Waters, Aquae (singular, Aqua; abbreviated, Aq.), are clear aqueous solutions of volatile substances. Two dissimilar classes of preparations come under this heading:

Aromatic Waters, *U.S.P.* (*Flavored Waters*) are generally saturated solutions of volatile oils. They are prepared by distilling the plant or oil with water, or simply by shaking the oil with distilled water. The quantity of active substance gives them a pleasant flavor without imparting noticeable therapeutic properties. The absence of alcohol makes them good solvents for salts. Their main use is as a pleasant vehicle for the conveyance of active substances. The *dose* of flavoring waters is practically unlimited (1.5 cc., 4 drachms U.S.P.). The U.S.P. includes waters of Anise, Camphor, Cinnamon, Peppermint, Spearmint, Rose and some others.

The second class of Waters (included under Liquores by the B.P.) are fairly strong *solutions of gases* (ammonia, etc.) prepared by passing the gas into water. Their doses are relatively small.

Solutions (*Liquor; Liq.*) are aqueous solutions of solid chemic salts or hydrates, made either by dissolving the pure salt directly in water by trituration or heat; or, more often, by chemic decomposition (simple and chemic solution). (The British Pharmacopoeia includes solutions of gases under this heading.) When used for special purposes, solutions receive special names. Injections (Injectio), Eye Waters (Collyrium), Washes (Lotio), Gargles (Gargarisma). *Collyria* should be isotonic with 1.4 per cent NaCl, and be neutral or buffered (Kopet, 1943). *Injections* are solutions or suspensions of drugs in water, saline solutions, oil, etc., for parenteral administration. The water must be "water for injection," U.S.P., *i. e.*, sterilized distilled water free from pyrogen, as determined by intravenous injection on rabbits. They should be preserved and dispensed in single containers, "*ampuls*" (ampulla), except for special circumstances. The pharmacopoeia lists *sizes* in which these and other dosage forms are "usually available."

For the *preservation of solutions* of organic substances intended for parenteral administration the U.S.P. permits the addition of not more than 0.5 per cent of chlorbutanol, cresol, phenol, sulfurous acid, sodium bisulfite or other suitable preservative. Not more than 0.85 per cent of sodium chloride may be present. The air in the container may be replaced by carbon dioxide or nitrogen. The presence and amount of any preservative in a solution intended for parenteral administration must be stated on the label of the container. The U.S.P. gives specific directions for *light-resistant containers* when these are necessary.

Mucilages (*Mucilago; Mucil.*) are aqueous solutions of gummy substances used as vehicles and demulcents. Since gums are insoluble in alcohol, mucilages are incompatible with this substance. They should be recently prepared because they are apt to mold.

Syrups (*Syrupus; Syr.*) are dense saccharine solutions of medicinal substances. The syrup serves as vehicle and preservative. Simple syrup is a nearly saturated solution of cane sugar, containing 85 Gm. in 100 cc., U.S.P.

Honey is sometimes used instead of cane sugar, makink a class of preparations called *mellita*, or *oxymellita* if acetig acid is added. *Confections* (*Confectio*; *Conf.*) are thicc medicated jams. They were formerly popular, but have now been almost abandoned. *Electuaries* were similar but somewhat thinner preparations.

Elixirs (*Elixir; Elix.*) are sweetened aromatic alcoholic liqueurs used, like the syrups, as flavoring vehicles. Their content in alcohol (about 25 per cent) is apt to lead to abuses, which must be kept in mind. The official Aromatic Elixir is flavored with orange peel, lemon, coriander and anise. *Iso-Alcoholic Elixir* (*Iso-Elixir*), N.F., is made by mixing a "low-alcoholic elixir" (about 10 per cent of alcohol) with a "high-alcoholic elixir" (about 75 per cent of alcohol) in such proportion as best dissolves the other ingredients of the prescription; the adjustment is left to the pharmacist.

Glycerites (*Glyceritum, U.S.P.; Glycerinum, B.P.; Glyc.*) are solutions in glycerin. Glycerin is a good solvent for many substances. It keeps well, and is especially useful for external application. It is less irritant than alcohol and is devoid of the pharmacologic action of this agent.

ALCOHOLIC SOLUTIONS

Alcohol is an outstanding solvent of volatile oils, alkaloids and resins. In prescribing, these should not be mixed with an aqueous solution. Alcohol is also a good preservative; it has therapeutic qualities which may or may not be desired.

Spirits (*Spiritus*, genitive *Spiritus; Sp.*) are alcoholic solutions of volatile drugs. They are all fairly potent. Flavoring spirits contain 10 per cent of the volatile oil. Their dosage is 1 to 2 cc., 15 to 30 minims. Spirits other than flavoring vary in strength and dose.

PREPARATIONS MADE BY EXTRACTION

In these, only a part of the crude drug is dissolved. They comprise the aqueous Infusions and Decoctions, and the alcoholic Tinctures and Fluid and Solid Extracts.

Infusions (*Infusum; Inf.*) are aqueous solutions of the soluble principles of vegetable drugs, obtained by pouring water on the moistened drug, letting it stand for half an hour and straining. They must be freshly made, and correspond to 5 per cent of the drug unless otherwise specified by the physician. **Decoctions** (*Decoctum; Dec.*) are made by boiling the drug with twenty parts of water for fifteen minutes, straining, and adjusting to correspond to 5 per cent of the drug. They spoil easily and must therefore be recently prepared. It is not practical to standardize them. They are virtually obsolete.

Tinctures (*Tinctura; Tr.*) are alcoholic or partly alcoholic solutions of the useful constituents of such drugs as are not wholly soluble in the menstruum; except *tincture of iodine, tincture of ferric chloride* and *tincture of tolu,* in which the solution is complete. Tinctures of potent drugs represent 10 per cent of the drug of minimium U.S.P. strength. Nonpotent drugs generally represent 20 per cent. Tinctures have the advantage that the dose is relatively large (about 2 to 4 cc. for the nontoxic); the quantity of solvent is sufficient to keep the principles in solution; the use of heat in the preparation is avoided. The greater number of tinctures are *prepared* by percolation; a few by maceration. The menstruum is alcohol or alcohol and water; acetic acid or glycerin is added in a few cases.

Aromatic spirit of ammonia is used in the *ammoniated tinctures. Detannated tinctures* are tinctures from which the tannin has been removed (as by powdered skin). They do not precipitate with iron salts. *Ethereal tinctures* are made with ethereal spirit, a mixture of 7 parts of ether and 3 parts of alcohol. Since some drugs are supposed to lose part of their activity by drying and keeping, a class of *Green Tinctures* made from the freshly collected green drugs has been introduced under the name of Tincturae Herbarum Recentium. *Wines* (*Vinum, Vin.*) are tinctures in which wines have been substituted for alcohol. They have inferior keeping qualities and are little used. *Aceta (Acet.)* are medicated vinegars, prepared by maceration with dilute acetic acid.

Fluidextracts, U.S.P.(Liquid Extracts, B.P.) (*Fluidextractum; Fldext.—Extractum Liquidum; Ext. Liq.*), are liquid alcoholic extracts, 100 cc. representing approximately 100 Gm. of the drug. The menstruum is sometimes modified by the addition of glycerin, acetic acid, etc. They are the most concentrated fluid preparations, but many are of doubtful value. Fluidextracts are usually prepared by percolation, the first four-fifths of the percolate being set aside, the remainder evaporated to the consistency of a soft extract, dissolved in the reserved portion, and menstruum added to make the required volume.

The simple ratio of drug strength has no special advantage in therapeutics, and has led to abuses such as preparing tinctures, infusions, etc., by the dilution of the fluidextracts. These dilutions often differ materially from the orthodox preparations. Concentration may sometimes be desirable to reduce the bulk of the dose, but is often secured at the cost of efficiency. The heat which must necessarily be used in their preparation may be detrimental. Precipitates are apt to form on standing, and may contain active principles. They are also much more subject to precipitation on mixture with other liquids, and the dose is usually so small that they require some such admixture.

Solid Extracts U.S.P. (*Extractum; Ext., Extractum Siccum; Ext. Sicc., B.P.*) are solid or semi-solid preparations obtained by evaporation of solutions of the medicinal principles of drugs. Some are dry, others of a "pilular" consistency, *i. e.*, like a pill mass. They are convenient for administration in solid form, *e. g.*, in pills, ointments, plasters, etc. Nearly all the potent, and most of the other, extracts are adjusted by the addition of glucose, etc., to four times the strength of the fluidextracts. "*Powdered extracts*" are dried, and mixed with sufficient diluent (lactose or starch) to give them the same strength as the solid extracts.

Most extracts are prepared by percolating and subsequent evaporation; the last and weaker portions of the percolate being evaporated first, to avoid the deleterious actions of prolonged heat on the main portion. Some of the extracts are obtained by evaporating the fluidextract. The menstruum is sometimes water or alcohol, or a mixture of both; acetic acid is added in some cases. The finished product is assayed, if possible, and adjusted to a definite standard by the addition of a diluent powder.

Artificial resins are precipitates obtained by mixing alcoholic solutions with water. Where they constitute the active principle, this is a convenient method of isolating it in a concentrated although somewhat impure form. Their strength is fairly constant. They are practically identical with the eclectic "resinoids." *Oleoresins* (*Oleoresina, Oleores.*) are extracts containing the resinous and oily constituents of the drug, and are obtained by evaporating ethereal, acetone or alcoholic percolates.

MIXTURES

Mixtures, in the wider meaning of the word, are fluids resulting from the mixture of fluids with other fluids or with solids. They comprise: Liniments, Mixtures and Emulsions.

Liniments (*Linimentum; Lin.*) are solutions of irritant drugs in oily, soapy or alcoholic vehicles, intended to be rubbed on the skin as counterirritants.

Mixtures (*Mistura; Mist.*), in the narrow meaning of the term, are generally suspensions of a solid in a liquid, sometimes by the use of a gummy substance; for heavy powders can not be evenly distributed in a light liquid without this aid. The B.P. also includes some emulsions under this title.

The *stabilizing, suspending or "deflocculating"* agents are protective colloids which raise the viscosity of the liquid and provide internal friction. *Acacia* is the suspending agent usually prescribed, employing up to 10 or 15 per cent of the powder, or 25 to 50 per cent of the Mucilage of Acacia. Acacia has the objection that it sours readily and tends to agglutinate bismuth subnitrate. Tragacanth, 5 to 10 per cent of the 6 per cent mucilage, is more efficient. Fantus advocated the (unofficial) *Karaya gum,* 1 per cent of the powder.

Emulsions (*Emulsio; Emul.*) are mixtures of a milky or creamy appearance, made by suspending fine droplets of a liquid in another liquid in which it is insoluble. The droplets constitute the internal or disperse phase. The fluid in which they float is the external or continuous phase. The dispersion or emulsification of the inner phase is effected and stabilized by the addition of emulsifiers, especially viscid colloids such as gums and protein substances, or agents that lower surface and interfacial tension, such as the bile salts, soap and saponin. These condense on the interphase of the liquids and form a pellicle around the droplets which prevents them from coalescing. The emulsion-state has considerable biological importance. Most pharmaceutical emulsions are of the oil-in-water type; "cold cream" is an example of water-in-oil emulsion. The object of *oil-in-water emulsification* is to break up the insoluble oil into fine particles and envelop each of these in a coating of the emulsifying agent. This allows dilution and the admixture of other substances, and facilitates absorption. Emulsification also improves the taste of undiluted oils, as cream is more pleasant than undiluted butter. Milk is a natural emulsion in which the butter fat is kept suspended by the casein. It may be taken as a type to which artificial emulsions should conform. The globules must be uniform and of about the same size as those in milk. A variety of substances may be used as emulsifier, especially gum acacia, tragacanth, karaya, agar, gelatin, yolk of egg, Irish moss, extract of malt, soap-bark and soap. The substance most commonly employed is gum acacia. This emulsifier is incompatible with more than 15 per cent of alcohol. Gum emulsions tend to ferment in a few days unless they are preserved by 10 per cent of alcohol or 1 per cent of benzoic acid. They should be kept in a refrigerator. Gelatin is wetted by both phases, the phase in large excess being external (R. M. Woodman, 1926).

In making the acacia emulsion, the oil is subdivided by trituration in the presence of the gum and enough water to make a thick mucilage. The friction against this viscid "nucleus" tends to tear the oil droplets apart; and as the smaller globules form, they are at once coated with the acacia film. The trituration must be brisk; for after the acacia films have formed it is much more difficult to break up the droplets further; nor must too much water be added until the emulsification of the nucleus is completed, for this would reduce the viscosity and the film formation. When the nucleus has been made, the films are adsorbed so firmly that they are not disturbed by contact with any quantity of water and may therefore be freely diluted. Two methods of emulsification are in common use: the Continental method, in which a nucleus is first formed from gum, oil, and water, and to which the remainder of the water may then be added; and the English method, in which a mucilage is first made, to which the oil and water are added in alternate small portions.

The *Continental method* deserves preference. To form a nucleus there should be used for each part of oil ¼ to ½ part of acacia and 1 part of water. Stir the oil with the acacia in granular powder, then add the water at once. The mixture of the oil and the gum must not be allowed to stand too long before adding the water, otherwise it will cake. In the *English method* the acacia, the amount of which should be half that of the oil, is rubbed up with an equal volume of water, and then small portions of oil and water are added alternately. If this addition should be done too rapidly, there is danger that the emulsion will separate or "crack." In *yolk emulsion,* the yolk of egg is triturated in a mortar and the oil and water are added alternately in small portions. One yolk suffices for from 1 to 2 ounces of oil. The yolk emulsions are incompatible with the same substances as gum emulsions and do not keep nearly as well. *Soap bark* has saponin for its emulsifying agent. It is not incompatible with any of the above-named substances, but has decided therapeutic properties which preclude its use in many cases. It is used in the proportion of 1 part of the tincture to 8 parts of the oil. Crude saponin (0.3:100 of oil) can also be employed. *Extract of malt* emulsifies its own weight of oil. It is used as the nucleus in the Continental method. *Solutions of alkalis* may be used for emulsification, since they form soaps, but they are usually not desirable. *Natural emulsions,* ready formed in nature, are milk, the yolk of egg, and some plant juices. *Gum resin and seed emulsions* are emulsions made from substances that contain their own emulsifier. Examples of such gum resins are ammoniac, asafetida and myrrh. The drugs are reduced to a coarse powder and water is added gradually. Seeds which yield such emulsions are poppy, hemp and almond.

SEMISOLID PREPARATIONS

Ointments (*Unguentum; Ung.*) are soft fatty masses for external application. They consist of the active ingredient and the base. The latter may be lard, petrolatum, wool fat (lanolin) or various mixtures. *Petrolatum* is a distillate of petroleum, either of amber color (flavum) or decolorized (album). *Wool Fat* (*Adeps Lanae*) is a mixture of cholesterol-like substances obtained from sheep's wool. It mixes with its own weight of water as a water-in-oil emulsion. This is of advantage for water-soluble salts, since these can be incorporated in the form of solution. It is also official as *Hydrous Wool Fat* (*Adeps Lanae Hydrosus, Lanolin*), in which about 27 per cent of water has been incorporated. This is rather stiff. A mixture of one part of anhydrous wool fat with three parts of petrolatum is miscible with twice its weight of water (Fantus). A mixture of equal parts of petrolatum and hydrous wool fat is a generally useful ointment base, as is also the U.S.P. *Unguentum*, consisting of white petrolatum and about 5 per cent each of wool fat and white wax. *Lard* rapidly becomes rancid. This tendency can be diminished by the incorporation of antiseptic substances. Benzoinated Lard is an attempt in this direction; but the dispensing of ointments in tin tubes is the most efficient protection against rancidity as well as against dirt. It should not be used if the ingredients of the ointment attack the metal.

The physical characters of the ointment bases, their melting point and their viscosity and adhesiveness, influence their availability for different purposes. When the ointment is to be applied by friction, for instance if it is to be rubbed in the hair follicles, a nonviscid base, such as lard, would be preferred. If a thick layer is to be kept in contact with the skin, the adhesive wool fat would be better. For a protective ointment, a thin layer, for instance of petrolatum, may suffice. The U.S.P. authorizes variations in the proportions of vehicle ingredients to adjust the consistence to climatic conditions. The nature of the base influences the *penetration of the ingredients* of the ointment into the skin. The absorption is high if the solubility of the substance in the epidermis is greater than its solubility in the ointment. Since this varies for each substance, no base is uniformly either favorable or unfavorable to absorption.

Deuterium tracer studies show that the fat, mineral oil and cholesterol of ointments are not at all absorbed (Czettsch-Lindenwald, 1943), and there is no good evidence that the ointment base acts as vehicle to carry substances through the skin (S. Rothman, 1943). The only visible penetration of fats is into the gland ducts (Strakosch, 1943; review, Calvery *et al.*, 1946).

Ointments are *prepared* by fusion, mechanical admixture or chemic reaction. In mixing ointments by fusion, that constituent of the ointment which has the highest melting point is first melted, and the others are then added in the order of their melting points. The active substance is added last, to obviate the prolonged action of heat upon it. Mechanical admixture is usually done on a slab or in a mortar. Powders must be as fine as possible.

Oculenta (*Oculentum*; *Oculent.*) are ointments for the eye. General formula, B.P.: 90 parts by weight of yellow soft paraffin and 10 parts by weight of wool fat plus a drug as stated by the prescriber. **Oleates** (*Oleatum*; *Oleat.*) are solutions of metals or alkaloids in oleic acid. They are used like ointments.

Cerates (*Ceratum*; *Cerat.*) are preparations similar to ointments but made of a firmer consistency by the addition of wax so as to remain semisolid at body temperature.

Plasters (*Emplastrum; Emp.*) are made by spreading on a thin cloth or leather support a mass or base which is hard at an ordinary temperature, but is softened and rendered adhesive at body temperature. They are applied for protection or counterirritation. A rubber composition is the base for most modern plasters.

The typical old-time plaster had for its base diachylon, Burgundy pitch or other resins. Diachylon is a lead soap made by boiling lead monoxide with olive oil and lard. To avoid the irritation resulting from the confinement of the secretions of the skin, plasters are sometimes made porous. Isinglass plaster is made by spreading a thick solution of isinglass on silk.

Chartae are medicated papers, *i. e.*, pieces of paper covered or impregnated with a medicinal substance. Charta Sinapis is used as a plaster, Charta Potassii Nitratis for fumigation.

Collodions (*Collodium; Collod.*) are solutions of pyroxylin (gun cotton) in a mixture of ether and alcohol, or in acetone. On evaporation of the solvent they form a film on the skin, and thus act like plasters. Collodion must not be brought near fire.

Poultices (*Cataplasma; Catapl.*) are used mainly for supplying heat. Linseed poultice may be taken as a type: It is prepared by pouring a cup of linseed meal into 2½ cups of boiling water, stirring constantly. The mush is spread thickly on a piece of flannel, folded so as to form a sack, and applied as hot as can be conveniently borne. Other pasty materials (flour, clay, etc.) are also used.

SOLID PREPARATIONS

Powders (*Pulvis; Pulv.*, Gen., *Pulveris*) are finely powdered drugs intended for external or internal administration. Those for internal use are generally folded in papers (*chartulae; chartul.*). Hygroscopic (deliquescent) substances, such as potassium acetate or citrate, cannot be prescribed in papers, nor substances that become fluid when mixed (such as camphor with chloral). If the dosage is less than 0.5 Gm. the powder should be diluted with sugar to this amount. If the dosage exceeds 1 or 2 Gm. and if it need not be accurate, it is more economical to dispense the powder in bulk, directing "dispense in box" or "dispense in bottle" (for hygroscopic substances), and to let the patient measure the quantity, on the assumption that a level teaspoonful would weigh about 5 Gm. Correction must be made for unusually light powders (quinine) and for heavy powders (bismuth subcarbonate).

In mixing compound powders, one should begin with the smallest ingredient and add the others in the order of their amount, triturating thoroughly after each addition. In dividing the powder, it is not always necessary to weigh out each powder. The object is often accomplished with sufficient accuracy by flattening the powder on a piece of paper, squaring off the edges, and dividing into a number of equal parts with a spatula. For more bulky powders, such as Seidlitz powders, measures are used. *For external use,* as for dusting powders, extreme fineness is the main desideratum. They should be mixed with a spatula and not in a mortar, since the former insures greater smoothness.

Triturations consist of one part of the medicinal substance and nine parts of lactose rubbed together to a fine powder. Their advantage lies in the greater ease in weighing out a comparatively large amount of substance. When no special directions are given, triturations are made of a strength of 10 per cent. *Eleosacchara* are triturations of volatile oils with sugar in the proportion of 1:30. They are used to flavor other powders.

Effervescent salts are dried salts, mixed with sodium bicarbonate and tartaric or citric acid so as to evolve carbonic acid when they are dissolved in water. This aids in disguising the taste. A number of these salts are official in the N.F.

DOSAGE FORMS

Capsules, tablets, lozenges, pills, etc., are used to divide the drug into definite doses, to avoid the inconveniences of dry powders, and to reduce the bulk. Care must be used in prescribing the dosage forms not to make them too large to be swallowed. The administration of drugs in compact solid form delays solution and absorption. This is especially true of old pills, in which the excipient may become so impervious that they pass unchanged into the feces; but it applies also to some tablets. A mere delay in solution may be an advantage if an intestinal action is to be procured; but difficultly soluble substances (salol, bismuth, etc.) should not be administered in these compact forms. Corrosive substances are unsuited for solid administration.

Capsules are small soluble containers, usually of gelatin, intended to be filled with the drug and swallowed. They furnish fairly accurate dosage and disguise the taste. Those used for powders consist of a body and a cap. In filling the capsules, the powder is divided into the requisite number of parts, forced into the body with a spatula, and the caps placed on. There is a range of sizes, but ordinarily not more than 0.25 Gm., 4 grains, should be placed in a capsule. Oils, up to 0.35 cc., eight drops, may be dropped into a capsule at the time of taking. Larger quantities of oils, 2 to 4 cc., can be taken in a "soft" capsule, but it is not convenient to prepare these extemporaneously.

Pill Masses in Capsules.—Capsules can be made to hold larger quantities of powders when these are made into pill masses. *Wafers* are thin sheets formed of a dried flour paste, in which the powder is enveloped. They are immersed in water and swallowed. They possess the advantage that larger quantities of the drug (up to 1 Gm.) may be administered. *Cachets* are wafers, molded into concave circular forms.

Tablets (*Tabellae; Tab.*) are small discs composed of medicated powders. They are convenient to administer, but are not easily made to order, so that the prescriber is confined to those carried in stock by the pharmacist. If this is not definitely known, it is advisable to direct "tablets or capsules."

Tablet triturates are prepared from the powdered drug and milk sugar or sugar, made into a paste with alcohol, pressed into molds, and dried. *Compressed tablets* are formed by strong dry compression. These are used like pills, or they may be chewed, or dissolved in water. Those of bitter taste may be coated with sugar or chocolate. By suitable choice of ingredients, they may be made acceptable to children (*Tabellae Dulces*, "Candy Medication," Fantus, 1912–1914). *Hypodermic tablets* are similar to the tablet triturates, especial care being exercised to facilitate quick solution. **Troches or lozenges** (*Trochiscus; Troch.*) are made by punching or cutting out circular or oblong disks from a mass made up from the active substance, sugar, and mucilage or fruit base. These are then dried in the air. They are usually intended for solution in the mouth, especially for throat medication. *Pastilles* are analogous preparations made with a sweetened gum-glycerin-gelatin base. **Lamellae** (B.P.) (*Lam.*) are thin gelatin discs, softened with glycerin, and impregnated with substances acting on the pupil. They are intended to be placed under the eyelids.

Pills (*Pilulae; Pil., U.S.P.*) consist of powders made into a plastic "mass" with a gummy or syrupy material "excipient" which keeps them more or less plastic. This *mass* (the B.P. "pill") is divided into suitable doses and rolled into small balls, to be swallowed. They can be prepared extemporaneously, and should not be kept too long, as they tend to harden, with decrease of solubility. Not more than 0.35 Gm. (5 grains) should ordinarily be prescribed in a single pill. If the pill is of larger size, it is called a *bolus*. Very small coated pills are spoken of as *granules*. The quantity of drug in the official pills is adjusted so as to make the average dose two pills. The choice of excipient may usually be left to the pharmacist.

Moist excipients are: glycerite of acacia or tragacanth thick flour paste, glycerin, syrup, confections or extracts· *Solid excipients* are: acacia, tragacanth, starch, althea, licorice powder, soap. For chemicals which are destroyed by organic substances the best excipient is formed by a mixture of petrolatum and kaolin. All excipients *delay absorption* somewhat. For iodide pills, Rieben, 1907, found the greatest delay with waxy and oily excipients, the least with vegetable extracts and syrups.

Pill-Coatings.—Pills may be coated with sugar, gelatin, chocolate, etc., to disguise their taste while being swallowed. The coatings tend to interfere somewhat with absorption. The simplest coating is to insert the pill into an ordinary gelatin capsule.

Enteric pills are coated with some substance (keratin, salol, stearic acid, formaldehyde-hardened gelatin, or shellac) which protects them from the gastric juice, but dissolves in the intestines. They would be useful when the drug is to act only after passing the stomach. They often fail to accomplish their purpose, for soluble drugs diffuse through them rapidly (Linossier, 1911) even if the coating is insoluble in the gastric juice, and water may be drawn in by osmosis and break the coating.

Goorley and Lee, 1938, experimented with a variety or enteric coatings and concluded that a mixture of castof oil, shellac and alcohol is the most satisfactory, especially if taken an hour or two before eating. Small pills and capsules pass into the duodenum much more easily than do the larger sizes. Improved directions for the salol coating of pills are given by Peacock, 1915; for stearic acid by Toplis, 1915. The latter claims that the stearic coating apparently fulfills its purpose. *Keratin* (a protein derived from horn, goose quill, etc.) was tried extensively, but it is totally unsuitable, since commercial specimens are largely soluble in artificial gastric juice (Puckner, 1911). *Formaldehydized capsules* are prepared by immersing the filled capsules in water containing 1 per cent of absolute formaldehyde, and drying. The capsules should become insoluble in acid pepsin solution, but remain soluble in 0.5 per cent sodium carbonate. The degree of insolubility s governed by the duration of the immersion (Scoville, 1915).

Suppositories (*Suppositorium: Supp.*) are cone-shaped masses of solid, medicated, usually fatty substances, intended for introduction into the rectum, vagina or urethra. They take the place of ointments for local treatment where these cannot be readily applied. Suppositories are made by incorporating the medicinal substance into a suitable base, and molding into masses of suitable shape and size. The base should be solid at the ordinary temperature and melt by the heat of the body. Such is cacao butter (Oleum Theobromatis), Glycerinated gelatin or a soapy base is also sometimes used, especially with urethral suppositories for which cacao butter would be too brittle. Rectal suppositories are usually made with sufficient base to weigh about 2 Gm. *Vaginal suppositories* are globular or oviform, and weigh about 4 Gm. *Urethral suppositories* are pencil-shaped, pointed at one end, measure 7 or 14 cm. and weigh 2 or 4 Gm. when made with glycerinated gelatin.

The "hot" process of making theobroma suppositories consists in melting cacao butter, adding the active substances, and pouring the mixture into cold molds. In the "cold" process the active substances are triturated with grated cacao butter and sufficient expressed oil of almond or wool fat to make a suitable mass, which is then rolled out and divided as for pills. They may also be formed by pressure. *Glycerin* is made into a suppository by a hard soap formed from stearic acid and sodium carbonate.

Ampuls (*Ampullae, Ampules*) are small, hermetically sealed glass flasks containing sterile solutions or suspensions of medicinal substances for parenteral injection. The glass must not give an alkaline reaction to water. Single dose ampuls, containing the desired dose generally in 1 or 2 cc. of water or normal saline, or larger quantities for intravenous injection, are closed by fusing the glass. "Multiple dose" ampuls, economical for hospital practice, are closed with a rubber diaphragm, which is pierced by the hypodermic needle.

PRESCRIPTION WRITING

A prescription is an order for medicine sent by a physician to a pharmacist. The first essential in such an order is that it be clear and free from errors. The use of Latin in writing prescriptions is an old tradition that should be abandoned; modern physicians and pharmacists are not at home in this language and are therefore more liable to make errors. The use of *abbreviations* is universal, but care needs to be used that they are not ambiguous.

Parts of the Prescription.—In writing a prescription, it is advisable to proceed in a definite order, which may guide the thought and protect against omissions and errors. The prescription is composed of four chief parts:

1. *The Superscription.*—The heading (℞). The ℞ stands for recipe, take thou. The stroke has been considered an ancient invocation to Jupiter; but probably it is simply a sign of abbreviation (McGuigan, 1913).

2. *The Inscription.*—The ingredients and their amounts. In these one should strive for simplicity, and multiply ingredients only if they are really indicated. If several are prescribed, they should be written in the following order, which places the most important first and the least potent last:

Basis: the principal substance.

Adjuvant: the substance which is used to aid the action of the basis.

Corrective: whose purpose is to modify or correct an undesirable action of the basis.

Vehicle: the indifferent substance used to dilute the active ingredients.

3. *Subscription.*—The directions to the dispenser. With liquid mixtures, the directions to the pharmacist may often be confined to M. (misce, mix).

4. *The Signature.*—The directions to the patient (for "signa," sign, label, abbreviated Sig. or S.). This is always written in English except for conventional abbreviations, so that the pharmacist may label the medicine with the words of the prescriber. The directions should be explicit and should include everything which it is necessary for the patient to know about the use of the medicine; unless the directions are unusually complicated, in which case they should be supplemented by written instructions. Verbal instructions are not safe. Medicines intended for external application should be plainly labeled to that effect, and when a medicine contains poison it should be so labeled, except when there is special objection to this.

The custom of having prescriptions "*refilled*" obtains in many localities. If the physician wishes to avoid this, he may write "non repetatur" on the prescription.

When the patient is very poor, the druggist may be invited to charge the lowest terms by writing P. P. (Pauperissimus) under the prescription. It is not just to do this if the physician himself receives a regular fee.

5. The prescription should also bear the signature of the physician, the date, and the name of the patient.

6. *Prescriptions for Habit-Forming Drugs.*—The federal law requires that prescriptions for cocaine or for opium or its alkaloids or derivatives must contain: the signature of the physician in full; his address; his registry number; and the name and address of the patient.

Such prescriptions cannot be "refilled." If their administration is to be continued the physician must write a new prescription.

The following illustrates a complete prescription:

Superscription.........	℞		Gm. or cc.
Inscription:	Basis	Codeine Sulfate	0.18
	Adjuvant	Ammonium Chloride	3.6
	Corrective	Ipecac Syrup	12.0
	Vehicle	Glycyrrhiza Syrup	36.0
Subscription:	Mix		
Signature:	Sig: A teaspoonful every two hours if needed for cough.		
	For Mr. Smith		John Doe, M.D.
January 1, 1947.			Reg. No. 12345

Forms of Administration.—If the medicine is to be used *internally*, it may be prescribed as:

Solution.—If the ingredients are soluble in water, alcohol or glycerin.

Mixtures or emulsions, i. e., suspended by acacia, if insoluble in water.

Powder.—If the substance does not have a very bad taste. These are preferred to the following preparations if the dose is bulky, or if the substance is to be dissolved in water before swallowing.

Pills, Capsules, etc.—If the substances are solid or semisolid, and possess a disagreeable taste; or if they are to act locally on the alimentary canal.

If the medicine is intended for *external use*, it may be prescribed as:

Plaster.—If the action is to be prolonged and superficial.

Ointment.—If the action is to be deeper, or briefer.

Lotions or Injections, Eye Waters, Gargles, etc.—If it is soluble in water.

Liniment.—If it is soluble in oil or alcohol.

The size of prescription is determined primarily by the number of doses. For instance, with the common routine of "three times a day," there would be 21 doses in a week. For liquids with a teaspoonful dosage, each one at 4 to 5 cc., this would come to 84–105 cc. (or ℥ iij in the apothecary system). The number may be rounded off so as approximately to fill the bottles in current use (15, 30, 60, 90, 125, 200, 400 cc.) (½, 1, 2, 3, 4, 6, 8, and 16 ounces). *For drop doses and eye waters*, the usual amount is 15 to 30 cc. (½ to 1 ℥); for teaspoon doses, 60 to 125 cc. (2 to 4 ℥); for *gargles, liniments and injections*, 60 to 150 cc. (2 to 6 ℥); *for lotions*, 120 to 200 cc. (4 to 8 ℥); *for tablespoon doses*, 150 to 400 cc. (6 to 16 ℥). *Pills* are prescribed in numbers of 5 to 25; *powders*, 1 to 24; *ointments*, 10 to 30 Gm. (½ to 1 ℥).

Calculation of Doses.—The prescriber generally starts with the dose to be taken at one time, and either directs the pharmacist to "make six (number) such doses" (fac tales doses numero sex); or else the single dose is multiplied by the number of doses, which is simple enough in the metric system, but more complicated in the apothecaries'. In either case the quantities are generally rounded off to a convenient number; a latitude of 10 per cent of the total falls quite within the ordinary variation of physiological response. Objection is sometimes made to the writing of the single dose and leaving the arithmetic of multiplication to the pharmacist, as a "lazy man's device." In fact, however, it protects the patient; for arithmetic is more safely performed in the quiet atmosphere of the prescription counter than under the stress and diversion of the bedside. In either case, the pharmacist is expected to check the doses of the ingredients, and not to dispense a prescription containing an *unusual dose of a powerful poison* without convincing himself that the physician prescribed this intentionally. While this does not lessen the responsibility of the physician, it is a desirable safeguard. To avoid delay, it is customary to mark large doses in such a way that the pharmacist will have no doubt that they are intentional. Thus: Tr. Digitalis, 15 cc. or 15 cc.! or 15 cc. Q. R. (quantum recte); or better to write out the words in full: 15 (fifteen) cc.

Percentage Solutions.—According to the U.S.P., when the expression "per cent" is used in prescriptions without qualification, it is to be interpreted to mean: for solutions of solids or gases in liquids, weight in volume; for solutions of liquids in liquids, volume in volume. The slight change in volume due to variations in room temperature and the trifling difference between the volume of the cubic centimeter and the milliliter may be disregarded.

The Need of Practice in Prescription Writing.—The construction of a prescription is based on simple principles which are easily memorized; but their application requires some practice.

The student who would master this subject should not rest content with doing the few exercises which can be given him in class. As he studies each drug, or as he reads up the treatment of diseases, he should himself compile such prescriptions as the subject suggests. This will aid him not only in prescription writing, but in pharmacology and therapeutics as well. It is only in this way that he can acquire the necessary self-confidence and skill. In this home practice, method and detail should be cultivated, for in these lies the secret of the art. The following rules may prove helpful:

Routine Construction of Prescriptions.—When writing a prescription for a given condition, set down, first, the name of the best remedy. Ask yourself whether there is any other drug which may be employed to aid or usefully modify the condition. Put this down also.

Then consider in which form the medicine should be administered, whether as liquid, powder, salve, etc. This will usually determine which preparation of the ingredient is to be employed. Put this down.

Then ask yourself what may be added to render the mixture agreeable to the patient. Add the vehicle. When this is written, all the ingredients will be represented.

Now look over this carefully and see that there are no incompatibilities and that the constituents are soluble if the mixture is to be a liquid. Write the directions to the dispenser. Assure yourself that the meaning is clear, the writing legible, and the abbreviations not ambiguous (the U. S. P. and the N. F. give official abbreviations). Decide how many days the mixture is to be taken, and how many doses a day (on the basis of sixteen hours to the day). Decide whether the dose of the total mixture is to be a teaspoonful, tablespoonful, etc. By multiplying the total number of doses with the size of the single dose, ascertain the approximate size of the mixture. Round this off to a convenient figure. If the prescription is to be of the "make X such doses" model, write after each ingredient the quantity of the single dose. If the total quantity is to be calculated, multiply the single dose of each ingredient by the total number of doses (again reducing the quantities to round numbers, unless the constituent is very potent). Check the doses. Write the directions to the patient. Consider whether a *non repetatur* is advisable. Affix your signature, the date, and the name of the patient. This finishes the prescription. Look over the result carefully in the same order. It is very important to use *legible handwriting*. It is astonishing, in view of the dire results that may follow, how often this self-evident rule is disregarded. The same remarks apply to *abbreviations;* it is necessary to make these in such a way that they cannot possibly be misinterpreted. A useful aid in acquiring practice in writing prescriptions is to look over a druggist's prescription file.

Simplicity in Prescription Writing.—Prescriptions were formerly written with many ingredients, with the hope that among these some might fit the patient. As medicine has become more scientific, it has aimed at simplification; prescribing several drugs only when there is evidence that this gives useful results. This makes it more feasible to watch and to control the effects, and incidentally makes it easier to avoid incompatibilities. When it is necessary to prescribe at the same time drugs which differ markedly in quickness of action, absorption or elimination; or habit-producing drugs with others that will presumably be used for longer periods, these should be administered in separate prescriptions. If the prescription includes a number of mixtures, each containing several ingredients, such as the numberless preparations put on the market by many firms, the result is, of course, as much a "shot-gun" prescription as if the prescriber had enumerated all the ingredients.

Non-Prescription Orders.—Pharmacists make a professional service charge on prescriptions above the "over-the-counter" cost. If the physician deems it justifiable to avoid this charge to the patient, for commercial articles, he may write the English name and the quantity ("Absorbent cotton, 1 lb."; "Cod liver oil, x brand, 1 pint"), but he must not sign it with his name or initials, for this would make it into a prescription, *i. e.*, an order from a physician to a pharmacist. Preparations which must be compounded extemporaneously will generally be treated as a prescription, even if they are not signed.

PRESCRIPTION LATIN

The inscription and the subscriptions are still often written in Latin, but this is not compulsory and indeed generally not advisable.

Advantages of Latin.—The use of the Latin names of drugs is generally urged because they are more definite and concise, and less liable to change than common names, and because they serve to keep the patient in ignorance of the nature of the drugs. This is sometimes desirable, *f. i.*, to guard against drug habits. The Latin names of the addiction drugs are, however, so close to the English names that they would generally be recognized; the object is more effectively secured by other means. Similarly, the official English names are equally definite. As a matter of fact, less than 5 per cent of the U.S.P. "Latin" names are really classical Latin (Oldberg, 1910). In the directions to the dispenser, Latin has no advantage, except in the brevity of the customary abbreviations. Indeed, unusual Latin terms are likely to lead to mistakes (Fantus, 1916).

Grammatical Rules for Latin Prescriptions.—The superscription, ℞ (recipe: "take thou"), requires the name of the substance to be in the genitive, if the quantity is given, the quantity itself being in the accusative (though, of course, rarely written out in full). When the quantity is not given, the name of the substance is to be placed in the accusative. Adjectives agree with their nouns in gender, number and case.

The following rules for the formation of the genitive case will be found valuable ("Mann's Manual"):

Nouns ending in a *form the genitive in* ae; as Quinina, Quininae. *Exceptions:* Aspidosperma, Physostigma and Theobroma form the genitive in *atis. Folia* is plural; genitive, *foliorum.*

Nouns ending in us, um, os, on, *form the genitive in* i; as Conium, Conii. *Exceptions:* Rhus, gen. Rhois; Flos, gen. Floris; Fructus, Cornus, Quercus, Spiritus, do not change.

All other nouns of whatever termination make the genitive in s, *or* is, *f. i.,* Elixir, gen. Elixiris.

Some lengthen the termination thus:

as, genitive *atis* (Acetas, Acetatis)
is, genitive *idis* (Anthemis, Anthemidis)
o, genitive *onis* (Persio, Persionis)
x, genitive *icis* (Cortex, Corticis)

Exceptions: Mas, gen. Maris; Phosphis, Sulfis, etc., gen. itis; Mucilago, gen. Mucilaginis; Solidago, gen. Solidaginis; Pulvis, gen. Pulveris, etc. The following words do not change in their genitive: Buchu, Cannabis, Catechu, Condurango, Cusso, Digitalis, Hydrastis, Jaborandi, Kino, Matico, Sassafras, Sago, Sinapis, Gambir, Sumbul.

The accusative is rarely employed. It is formed according to the following rules: *Nouns singular ending in* a *are feminine, and make the accusative singular in* am *and the plural in* as. Example: Drachma, acc. sing. Drachmam, pl. Drachmas. *Those ending in* um *or* us, *make the accusative singular in* um. *The accusative plural of those in* us *is* os, *and of those in* um *is* a. Those in *us* are masculine, those in *um* are neuter: Congius, acc. sing. Congium; acc. pl. Congios. Granum, acc. sing. Granum; acc. pl. Grana. *Those whose genitive ends in* is, *form the accusative in* em, *plural* es.

The student must not forget that adjectives change their endings.

The following *prepositions* are frequently used and command the following cases:

ad	to	accusative
ana[1]	of each	genitive
cum	with	ablative
in	into	accusative

The following **Latin words and phrases** occur frequently in prescriptions:

ad	to, up to
ad libitum	at pleasure
adde	add (thou)
ana (āā)[1]	of each
aqua bulliens	boiling water
aqua destillata	distilled water
aqua fervens	hot water
aqua fontana	spring water
bene	well
bis in die (b.i.d.)	twice daily
cape, capiat	take, let him take
capsula	capsule
charta	a paper (medicated)
chartula	a small paper for a powder
cibus	food
cochleare magnum	a tablespoon
cochleare parvum	a teaspoon
cola, colatus	strain, strained
collyrium	an eye wash
congius (C.)	a gallon
cum	with
dilute, dilutus	dilute (thou), diluted
dimidius	one-half
dividatur in partes aequales	let it be divided into equal parts
divide (Div.)	divide (thou)
dividendus	to be divided
dosis	a dose
fac, fiat, fiant (ft.)	make, let be made, let them be made
fac tales doses	make such doses
filtra	filter (thou)
gargarisma	a gargle
gutta, guttae (gtt.)	a drop, drops
haustus	a draught
hora	an hour
hora decubitus	at bed time
hora somni	just before going to sleep
instar	like (with genitive)
lac	milk
libra (lb.)	a Troy pound
magnus	large
mane primo	very early in the morning
misce (M.)	mix
mitte	place, send
more dictu	as directed
non repetatur	do not repeat
numerus, numero (No.)	a number, in number
octarius (O.)	a pint
ovum	an egg
pars	a part
partes aequales (P. æ.)	equal parts (governs genitive)
parvus	small
pilula (pil.)	a pill
pone	place
pro re nata (p.r.n.)	according to circumstances, occasionally
pulvis (gen. pulveris)	a powder
quantum sufficiat (q.s.)	as much as is necessary
quaque die	every day
quaque hora	every hour
quater in die (q.i.d.)	four times a day
secundum artem	according to the usual practice
semel in die	once a day
(cum) semisse (ss.)	and a half
signa	sign
sine	without
si opus sit (s.o.s.)	if necessary
solutio	a solution
solve, solutus	dissolve, dissolved
statim	immediately
talis	such
ter in die (t.i.d.)	three times a day
tere simul	rub together
tritura	triturate
vitellus	the yolk (of an egg)

◆

METROLOGY

A ready working knowledge of weights and measures is indispensable in prescribing.

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[1] From the Greek, "at the rate of."

Formerly every country and some cities had their own system of weights and measures, resulting in endless confusion and loss of time. This still exists to some extent. In the United States and Great Britain no less than five different systems are in common use. In the United States, however, there is a strong trend toward the use of the metric system in prescribing. This is stressed by the U.S.P. and N.F. and employed exclusively in the N.N.R. and in the medical services of the Government. The metric system, which originated in France near the close of the eighteenth century, has been adopted in science to the exclusion of all others, and has advantages which should cause all other systems to be discarded. Since, however, the common systems are still used in many hospitals and journals, these must also be mastered, and the conversion of the systems practiced.

The metric system is based on the decimal system and has for its unit the measure of length, the meter (M.).

This was intended to be a natural unit, viz., the ten-millionth part of the distance from the pole to the equator of the earth at a particular meridian. Subsequent measurements have given a slightly different value to this distance. The meter is therefore an arbitrary standard—the length of a platinum bar, the original of which is preserved in Paris.

The meter is divided into 10, 100 and 1000 parts, called, respectively, decimeter (dm.), centimeter (cm.) and millimeter (mm.). The thousandth part of a millimeter is a micron (μ). The contents of a cube whose edges measure a decimeter, or 10 cm., form the unit of capacity, practically equivalent to the liter (L.). The thousandth part of this is a cubic centimeter (c.cm. or, briefly, cc.; also termed a "milliliter" or "*mil.*"). The unit of weight is the weight of a liter of distilled water at 4° C. *in vacuo:* this is the kilogram (Kg.). A thousandth part of this is a gram (Gm.). The tenth part of the units is expressed by prefixing the Latin numeral deci; one-hundredth, centi; one-thousandth, milli.

Thus:

1000 Gm. = Kilogram (Kg.)[1]
1 Gm. = Gram (Gm.)
0.1 Gm. = decigram (dg.)
0.01 Gm. = centigram (cg.)
0.001 Gm. = milligram (mg.)
0.001 mg. = microgram (μg; but not to be abbreviated in prescriptions)

In quantities including several denominations only one unit is used: thus, 1.234 Kg. would be read as 1234 Gm. Fractions below 0.1 Gm. are usually written as milligrams (99 mg. instead of 0.099 Gm.). The quantities are always denoted by Arabic figures placed before the appellation. Fractional parts are always converted into a decimal fraction. In continental Europe liquids are usually weighed.

Common Systems of Weights and Measures.[2]—The denominations are as follows:

APOTHECARIES' OR TROY WEIGHT

(USED IN PRESCRIPTIONS)

Grain (gr.)
[Scruple (℈) = 20 gr.]
Drachm[3] (ʒ) [= 3℈] = 60 gr.
Troy ounce (℥) = 8ʒ = 480 gr.
[Troy pound = 12℥ = 5760 gr.]
(℥j of water under standard conditions[4] measures 504.83 minims.)

AVOIRDUPOIS OR IMPERIAL WEIGHT

(A SYSTEM USED IN COMMERCE)

Grain = same as Troy grain.
Ounce (oz.) = 437½ grains.
Pound (lb.) = 16 oz. = 7000 grains.
Ton = 2000 lb.

UNITED STATES APOTHECARIES' OR WINE MEASURE

(USED IN UNITED STATES FOR BOTH PRESCRIPTION AND COMMERCIAL PURPOSES)

Minim (♏ or min.) (approximately equal to 1 drop or to 1 grain of water—more exactly, 0.95 grain).
Fluidrachm (fl ʒ) = 60 ♏.
Fluidounce (fl ℥) = 8 fl ʒ = 480 ♏ (fl ℥ j of water under standard conditions[4] weighs 456 2/5 grains).
Pint (pt., or Octarius, O) = 16 fl ℥ = 7680 ♏.
Quart (qt.) = 2 pts. = 32 fl ℥.
Gallon (gal., or Congius, C) = 8O = 128 fl ℥ = 61,440 ♏.
A gallon holds 231 cubic inches.

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[1] Some authors begin all abbreviations with capitals; others use capitals for Gram, Liter, Meter and their multiples; and small letters for fractions.

[2] Those in square brackets are practically obsolete

[3] Also spelled dram.

[4] At 4° C. in vacuum.

Another system of liquid measure is in use in *Great Britain,* and must not be confused with the American system. It is the

IMPERIAL MEASURE

		UNITED STATES SYSTEM
Minims (min.)	=	0.96 ♏
Fluidrachm (fl. dr.)	= 60 min.	= 0.96 fl ʒ
Fluidounce (fl. oz.)	= 8 drachms	= 0.96 fl ℥
Pint (O)	= 20 fluidounces	= 1.2 O
Gallon (C)	= 8 pints	= 1.2 C

In writing the apothecaries' measure in prescriptions, the numbers are written in the Roman system and placed after the appellation. Thus, gr. xx, not 20 gr. The ones are always dotted, and the last one is formed like a j: thus ʒiij, ℥vj. The fl. before the sign is often omitted with liquids. Fractions are written as common fractions: gr. 1/10, not gr. 0.1.

Popular measures are formed of utensils commonly found in the household, and are inexact. They should be displaced by graduated medicine glasses. Spoons are supposed to be filled so that the fluid stands level with the rim.

The usually accepted equivalents of these measures are:

1 drop (gtt.)	= 1 minim[1]	= 0.05 cc.
1 teaspoon	= 1 fl ʒ[2]	= 4 cc.[3]
1 dessertspoon	= 2 fl ʒ	= 8 cc.
1 tablespoon	= 4 fl ʒ (½ ℥)	= 15 cc.
1 wine-glass	= 2 fl ℥	= 50 cc.
1 tea-cup	= 4 fl ℥	= 125 cc.
1 tumbler	= 8 fl ℥	= 200 cc.
1 knifepointful (tableknife)	= 15 to 30 gr.	= 1.0 to 2.0 Gm.

Equivalents of Metric and Common Systems.—Doses and formulas may be transposed on the basis that 1 Gm. equals 15.4 grains; but errors of reckoning may have serious consequences. It is generally safer to use the following approximate equivalents which are sufficiently exact for prescription purposes:

APPROXIMATE EQUIVALENTS

1 Gm. } = 15.5 grains or minims
1 cc. }
1 milligram = 1/64 grain
1 Liter = 1 quart (+)
1 Kilogram = 2.2 lb.

1 grain or minim = 0.065 Gm. or cc.

1 drachm = 4.0 (−) or cc.
1 ounce = 30.0 (−) or cc.
1 pint = 0.5 Liter (−)

EXACT EQUIVALENTS—SPACE

1 meter = 39.370 inches
= 3 ft. 3.370 inches
= 1 yd. 3.370 inches

1 inch = 0.0254 M. = 2.54 cm.
1 ft. = 30.48 cm.
1 yd. = 91.440 cm.

CAPACITY (United States)

1 cc. = 16.23 ♏
1 L. = 33.815 fl ℥
= 2.113 pts.
= 0.2642 gal.

1 ♏ = 0.06161 cc.
1 fl ʒ = 3.7 cc.
1 fl ℥ = 29.574 cc.
1 pt. = 0.4731 L.
1 gal. = 3.7854 L.

CAPACITY (British)

1 L. = 1.760 pints
= 0.2209 gallons

1 pint = 0.5679 L.
1 gallon = 4.5435 L.

WEIGHT

1 mg. = 1/65 gr.
1 Gm. = 15.432 gr.
= 0.03527 oz. Av.
= 0.03110 ℥ Troy.
1 Kg. = 2.2046 lb. Av.

1 gr. = 64.8 mg. = 0.0648 Gm.
1 ʒ = 3.888 Gm.
1 oz. Av. = 28.3495 Gm.
1 ℥ Troy = 31.1035 Gm.
1 lb. = 0.4536 Kg.

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[1] The size of a drop varies according to the nature of the fluid and of the container; there may be from 50 to 150 to a fluidrachm. The U.S.P. specifies a standard dropper "adjusted to deliver 20 drops of distilled water weighing 1 Gm. at a temperature of 15° C." This would deliver about three times as many drops of alcohol, and about five times as many of ether or chloroform, per cc. Drops are indefinite and inaccurate with a standard dropper.

[2] Really from ½ to 2 fl ʒ.

[3] As a matter of fact, the actual capacity of teaspoons averages 5 cc. when filled level (Wilbert, 1905).

COLORING AND FLAVORING

These are used to make medicines more agreeable. Children may need to be bribed, but for adults it may suffice to remove the repulsive features so far as feasible, and this can generally be accomplished by relatively simple means. The most important of these is the form of administration. Small doses of powders may be given in capsules or tablets or in a spoonful of jelly. Large doses may be taken with cereal or in thick soup. The taste of water-soluble drugs is often best improved by simple solution, in half a tumbler or a tumblerful of water or mineral water, quickly swallowed and followed by a draught of cold water; or they may be taken in milk, tea or soup.

COLORING

Liquid prescriptions intended for internal administration should be clear if possible. The appearance may sometimes be improved by adding a coloring matter, which may prove useful through its suggestive element. The coloring agent must vary according to the nature, and especially the reaction, of the mixture. The usual colors for internal use are red, brown, and yellow. Aniline dyes should be avoided, except methylene blue and gentian violet for external preparations, and eosin, fluorescein and indigocarmine for identification, for instance, for local anesthetics.

The most useful pharmaceutical coloring agents[1] are:

For Red or Pink: *Solution of Amaranth*, U.S.P., a 1 per cent aqueous solution of amaranth, trisodium naphthol sulfonic acid, a synthetic vivid red dye, not changed by acids, intensified by sodium hydroxide.—*Tinct. Cudbear* (Tr. Persion, N.F.); red in neutral or acid, violet in alkaline solution. Used in proportion of about 1.5 per cent. Prepared from a lichen allied to litmus.—*Tinct. Cardamom Compound* (Tr. Cardam. Co., U.S.P.); colored with Cochineal; 50 per cent alcohol.—*Carmine Solution* (Liq. Carmin., N.F.); pink to deep red in alkaline solution (used in proportion of about 1 per cent), incompatible with acids. *Carmine* is used in powders, etc. (1:500). It is prepared from *Cochineal* (Coccus, U.S.P.), a dried scale-insect.—*Red Saunders* (Santalum Rubrum, U.S.P.), a wood, is used in Comp. Tinct. Lavender.

For Brown: *Fldext. or Elixir of Glycyrrhiza* (Licorice) (U.S.P.); not suitable for acids.—*Caramel* (Carbonized Sugar) (N.F.). Commercial caramel is generally made by heating glucose with a little alkali until the sweet taste is destroyed and a uniform dark mass results. It is probably a complex mixture. Caramel from cane sugar, according to Stolle, 1899, is a single substance, $C_{12}H_{18}O_9$, formed by the elimination of two molecules of water from sucrose. Caramel has been tried in diabetes, being apparently well tolerated (Grafe, 1914; Umber, 1915).

For Yellow: *Tinct. Hydrastis* (Tr. Hydrast., N.F.), or *Tr. Curcuma* (Turmeric); about 1 per cent. Tr. Curcuma precipitates with water, but sufficient remains in solution to impart a yellow color. An infusion of the root of Curcuma longa is used by West African natives to treat jaundice (G. W. Harley, 1941).—*Saffron* (Crocus, N.F.) has been used as abortifacient, but it apparently lacks this action and is practically nontoxic (Cevidalli, 1914). It is but slightly toxic to mice (Zipf and Bernebée-Jay, 1936)

FLAVORING

Suitable flavoring secures more effective cooperation of the patient and may be necessary to obtain the retention of the medicine in the stomach.

Patients may fail to take a disagreeable medicine, and the physician should be on the lookout for such cases. He may approximately control the amount taken by judging as to the quantity left in the container. If the patient carries the deceit further and pours away the appropriate amount of the medicine, and if the physician does not obtain the anticipated results, it may be well to prescribe some test medicine, such as salol (0.3 Gm.) or sodium iodide (0.5 Gm.), which can be detected in the urine.

The taste of liquid medicines may be improved by dilution, sweetening, demulcents, aromatics, alcoholics, acids, bitters and drugs which paralyze the taste endings. Several of these means may be combined. *Cooling of fluids decreases their taste.* The taste threshold is lowest between 34.5° and 37° C., increasing about a third for each 5° below and above this level (Hahn and Günther, 1932).

Simple dilution is often most effective for substances with disagreeable but not very intensive tastes, such as salts, alkalis and most hypnotics. These should be taken in a half-glass or glass of water, milk, tea or carbonated water. Flavoring syrups, which are usually prescribed as one or two teaspoonfuls, are diluted with water "to taste" at the time of taking.

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[1] The preparations of each class are generally arranged alphabetically under the crude drugs. The important preparations, which the student is expected to study, are marked.* In addition to these, he should glance over the descriptions of the corresponding crude drugs.

"U.S.P." stands for preparations official in the United States Pharmacopoeia; "B.P.," British Pharmacopoeia; "N.N.R.," New and Nonofficial Remedies; "N.F.," National Formulary; "B.P.C.," British Pharmaceutic Codex.

The following abbreviations are used in connection with solubilities. Alc. = alcohol; glyc. = glycerin; eth. = ether; chlorof. = chloroform. The figures refer to the part of the solvent required to dissolve 1 part of drug (*f. i.*, 1:0.5 = 1 part of drug dissolves in 0.5 part of solvent). The solubilities refer to 25° C. (room temperature), unless otherwise stated.

The Most Important Flavors.—The following will be found to be generally sufficient: *To disguise bitter taste:* Aromatics (Tr. Cardamom Co.; Aromatic Elixir; Red Elixir; Orange Syrup; for children, Syr. Glycyrrhiza, Syr. Tolu, Anise Water, Balsam. *To disguise acrid taste:* Aromatics as above; also syrups, acacia, acid flavors (Syr. Orange). *To disguise salty or alkaline taste:* Dilution with simple, carbonated or aromatic water or milk. *To disguise oily taste:* Aromatics (Oil or Spirit of Peppermint, lemon, orange, wintergreen or almond, according to personal preference). *For insipid drugs:* Aromatics and acids (Syr. Orange).

The popularity of flavors changes from time to time. In a survey of students H. N. Wright, 1937, found the order of preference as follows: highest; Syrup Cacao (chocolate) and Syr. Raspberry, N.F.; then, Syrups of orange, cherry, sarsaparilla, citric acid; least, Syrup of wild cherry, aromatic elixir, and glycyrrhiza.

Incompatibles.—Fruit syrups are discolored by alkalis, even by methenamine or sodium citrate.

SWEETENING AGENTS

The property of sweetness, like that of bitterness, is found in a variety of substances. It is a common characteristic of the sugars, which differ, however, in degree. The otherwise rather inert saccharin has most intense sweetening power. Licorice owes its taste to a glucoside, glycyrrhizin, which is sweet in alkaline, but not in acid liquids. Other substances of sweet taste are glycerol and chloroform. Although all these are "sweet," there are qualitative as well as quantitative distinctions in their taste. Attempts to connect sweetness with the chemic structure have not been very successful (C. J. Carr *et al.*, 1936).

The usual agent for sweetening liquids is sucrose, in the form of its saturated watery solution or "syrup." This is improved by the presence of flavors with more distinctive taste, such as glycyrrhiza, tolu, and orange; or a mixture of aromatics and alcohol, as in the Aromatic Elixir. Honey, fruit syrups, jams and jellies are flavors that can be added in the household. Saccharin is used for diabetic patients, and in pill coating. Powders may be sweetened with lactose, which also assists in grinding the powders because of its hardness. Sugars are foods, and dextrose and levulose, lactose and maltose will be described in that connection.

Intensity of Sweetening Power.—If that of sucrose is taken as 1, then levulose is about 1¾; glucose, ¾; maltose and galactose, ⅓; lactose, ⅙ (Beister *et al.*, 1925). The ratios differ somewhat for individuals and alter with the *concentration.* This increases the sweetness of fructose more than of sucrose. Glucose and sucrose together give a sweeter taste than the sum of their separate sweetness (A. T. Cameron, 1943). The sweetness of various substances and their mixtures is reported by Cameron, 1945.

Taste Blindness—Phenylthiocarbamide.—Crystals of this and other thiocarbamides are intensely bitter to some persons; to others they taste sour or peppery or astringent; to others again they are tasteless. The "dual taste reaction" accompanies the grouping: —NH=C=S (C. Y. Hopkins, 1942). A. F. Blakeslee and Salmon, and independently L. H. Synder, found that the nontaste is a recessive Mendelian character. The difference is quantitative, for saturated solutions are bitter also to nontasters. The crystals are less tasted partly because of different solubility in different salivas. There is no close relation to the acuity of the bitter taste of quinine or picric acid (which also show wide variations), nor is there any relation to the appreciation of acid or sweet taste, or odors. The differences illustrate that "different people live in different worlds, therefore, so far as their sensory reactions are concerned" (A. F. Blakeslee, 1931).—Phenylthiocarbamide produces pulmonary edema in rats (Richter and Clisby, 1942; see Index).

PREPARATIONS.—*Syrup of Citric Acid,* U.S.P. (Syr. Acidi Citrici), a 1 per cent solution flavored with Tincture of Lemon, an alcoholic extract of fresh Lemon Peel.

***Aromatic Elixir,** U.S.P. (Elix. Aromaticum; Simple Elixir), a syrup containing about 23 per cent of alcohol and flavored with aromatics (Comp. Spir. Orange).

***Syrup of Orange,** U.S.P. (Syr. Aurantii), flavored with tincture of sweet orange peel and contains *one half per cent of citric acid.*

***Fluidextract of Glycyrrhiza,** U.S.P. (Fldext. Glycyrrhizae; Fluidextract of Licorice Root), a watery extract of *glycyrrhiza* (licorice root), the dried rhizome and roots of varieties of Glycyrrhiza glabra. It is extracted with hot water; a small quantity of ammonia is added to increase the solubility of the sweet principle, *Glycyrrhizin,* which is incompatible with acids. The solution is evaporated and mixed with alcohol to about 22 per cent by volume. Dose, 2 cc., ½ drachm.—*Syrup of Glycyrrhiza,* U.S.P., is a mixture of one part of the fluidextract with three parts of syrup and small amounts of oils of anise and fennel. It is a good vehicle for quinine and other bitter substances.—*Elixir of Glycyrrhiza,* N.F., consists of one part of the fluidextract and seven parts of Aromatic elixir.

***Syrup,** U.S.P. (Syrupus; Sirup, Simple Syrup), is a concentrated aqueous solution of sucrose containing 85 Gm. per 100 cc. of syrup. *Sucrose,* U.S.P. Saccharum, Sugar, from cane or beets or other sources, is very sol. in water (1:0.5) and slightly sol. in alc. (1:170). Used for sweetening powders, for the administration of volatile oils (oleosacchara), for preparation of syrups, elixirs, etc. Simple syrup is miscible with water or alcohol. Official flavoring syrups include syrup of Citric Acid, Glycyrrhiza, Orange, Orange Flowers, Sarsaparilla Compound (used especially for potassium iodide), Tolu Balsam, Wild Cherry (bark).

SACCHARIN

This substance, $C_6H_4{\cdot}SO_2{\cdot}CO{\cdot}NH$, sold also under various trade names, is the anhydride of ortho-sulfamido-benzoic acid (the para-isomer is not sweet). In common with a number of other benzene derivatives, it has an intensely sweet taste, even in very dilute solutions. It passes through the body almost quantitatively unchanged, 75 to 90 per cent being excreted by the urine within twenty-four hours, and the remainder in the feces. Consequently it has a very low toxicity. Its administration in amounts fifty times those ordinarily taken as sugar substitute does not produce any significant effects (Lehmann, 1890). The only objectionable feature is a disagreeable sweet or bitter aftertaste, noticeable generally only with large doses or by especially susceptible individuals (Pavy, 1888). It increases gastric acidity, but not sufficiently to be contraindicated in hyperchlorhydria or duodenal ulcers (H. Staub, 1937).

Small doses, up to 0.3 Gm. per day, continued for months, produce no deleterious effects, so far as ascertainable by available methods of investigation. Large doses, 0.75 to 1.5 Gm. per day, are also practically harmless, except for occasional minor disturbances of digestion (Herter and Folin, 1911). Single doses of 5 Gm. have been given without much effect (Adduco and Mosso, 1887). With 5 to 25 Gm. per day, or 100 Gm. as one dose, there may be anorexia, intestinal irritation and diarrhea, but no more than with equal doses of table salt (review, H. Staub, 1937). Lehmann, 1929, raised three generations of mice on a diet containing saccharin corresponding to about 13 Gm. for man per day.

Uses.—Saccharin is used as a substitute for sugar in diabetes (tablets of 0.003 Gm., ½ grain, replace an ordinary lump of sugar); as flavoring agent and adulterant of sweet foods; and as a mild antiseptic in fermentative dyspepsia (0.2 Gm., 3 grains, several times daily). Saccharin itself is but little soluble in water, but its sodium salt, "*soluble saccharin,*" dissolves readily. It may be prepared by adding ½ part of sodium bicarbonate.

The sweetening power is 300 to 500 times as great as that of cane sugar. It is perceptible in dilutions of 1:100,000; 1:10,000 is agreeably sweet; with 1:1000 it becomes bitter and disagreeable. Even with the more dilute solutions the quality of the taste is somewhat different from that of sugar, and on continued use the persistent aftertaste becomes objectionable.

Effects of Continued Use.—Long-continued and detailed investigations were made for the Referee Board by Herter and Folin, 1911; Herter administered the sodium salt, Folin the free saccharin, in "small" doses to 0.3 Gm. per day, and "large" doses of 0.75 to 1.5 Gm., corresponding in sweetening power to 150 Gm. and to 375 to 750 Gm. of cane sugar respectively. The small doses produced no discoverable effects. The large doses were also negative except that occasionally there were slight hyperacidity and indications of slight increase of intestinal putrefaction. *In vitro*, the efficiency of all the digestive ferments is not altered by the concentrations which might occur in the body (except by the acidity of free saccharin, a factor which had been neglected in some of the earlier investigations). The *antiseptic action* is slight. The older literature contains reports of digestive and other disorders, especially after continued use (v. Jaksch); but these observations were not made with the same degree of accuracy.

The toxicity for animals is very low (Adduco and Mosso, 1887). Matthews and McGuigan observed depression, stupor, convulsions and nephritis. Herter, administering soluble saccharin to rabbits by stomach, found no effects with 4 to 5 Gm. per kilogram; double this dose was fatal in two hours, the autopsy showing violent gastrointestinal irritation. Kusaka, 1926, claimed to have produced gastroenteritis in rabbits; and central paralytic effects and chronic toxic phenomena in rabbits and mice.

Saccharin for Measurement of the Circulation Time.—This may be gaged by the time of the appearance of sweet taste after a solution of soluble saccharin is injected into the cubital vein: Three Gm. are dissolved in 3 cc. of warm water, and 2.5 cc. injected as rapidly as possible The taste is normally noted in 8 to 16 seconds (A. M. Fishberg *et al.*, 1933). Care must be taken that the solution does not escape into the subcutaneous tissue, as its alkalinity produces necrosis (Leinoff, 1935).

Use of Saccharin in Foods.—No serious damage need be apprehended from the quantities of saccharin which would ordinarily be used. The peculiar taste may become repulsive and diminish appetite. For this reason and because saccharin has no food value, its indiscriminate use as a sweetening agent should be condemned, except in cases in which sugar is inadmissible.

PREPARATIONS.—***Saccharin Sodium,** U.S.P. (Saccharinum Solubile; Soluble Gluside, Soluble Benzosulfinide), occurs as colorless prisms or white, crystalline, odorless powder; very sol. in water (1:1.5) and alc. (1:50). *Saccharin* is less sol. in water (1:290), more sol. in alc. (1:31), and easily sol. in alkalis. Dose, 60 mg. have the sweetening power of 30 Gm. of sucrose as sweetening agent in diabetes, etc., 1:10,000 (0.1 Gm. per liter, 1/20 grain per ounce); or 0.03 Gm., ½ grain, in place of an ordinary lump of sugar. *Saccharin Sodium Tablets*, U.S.P., are usually available as 15, 30 and 60 mg. (¼, ½ and 1 grain).

AROMATIC WATERS, SPIRITS, OILS AND TINCTURES

Aromatic Waters are miscible with water or alcohol. Their dose is ad libitum. *Aromatic Spirits* are used in alcoholic and oily liquids, in the proportion of 2 per cent. They are immiscible with water. *Aromatic Oils* may be used for flavoring alcoholic or oily liquids, in the proportion of 0.2 per cent The spirits, however, are generally preferred. *Aromatic Tinctures* are used like the spirits. None of the simple tinctures are especially important.

Preparations.—***Compound Tincture of Cardamom,** U.S.P. (Tr. Cardamomi Composita), is flavored with cardamom, cinnamon and caraway; colored red by cochineal; and contains about 45 per cent alcohol. Dose, 4 cc., 1 drachm.

***Cinnamon Water,** U.S.P. (Aq. Cinnamomi), is a saturated solution of cinnamon oil (water distilled from the bark, B.P.). Dose, 15 cc., 4 drachms.

***Peppermint Water,** U.S.P. (Aq. Menthae Piperitae), is a saturated solution of the oil of peppermint. Dose, 15 cc., 4 drachms.

***Rose Water,** U.S.P. (Aq. Rosae), is a half saturated watery distillate of the fresh flowers of Rosa centifolia; used to perfume lotions, etc.

ERIODICTYON (YERBA SANTA)

Extracts of the leaves of this plant disguise bitter taste (not sweet, salt or acid taste). Fantus *et al.*, 1933, attribute this to the adsorption of basic alkaloids; but it is said to be effective also against neutral principles. One cc. of the fluidextract covers the taste of 0.012 Gm. of quinine sulfate or 1.5 Gm. of quassia. It is incompatible with acids and with excess of alkali. Its tannic acid discolors with iron salts.

Preparations.—*Eriodictyon,* U.S.P. (Yerba Santa) consists of the dried leaves of Eriodictyon californicum. Used as the fluidextract in a dose of 1 cc., 15 minims; precipitated by water.

Other plants which suppress taste are: Gymnema sylvestre; Bulmenia dulcifica, and Phrynium Danieli. They are not practically effective.

Gymnema.—The leaves of this plant contain gymnemic acid, which destroys bitter and sweet taste, not acid or salt. The paralysis of sweet taste lasts for two hours. Gymnema has been used in *diabetes mellitus.* R. N. Chopra, Bose and Chatterjee, 1928, reported that it has no effect on the blood sugar; but Maskar and Caius, 1930, who studied its constituents and activities, claim that it produces hypoglycemia, which they attribute to increased production of insulin by the pancreas.

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SOLUBILITIES

The following compilations of the solubility of the substances usually prescribed may be found useful. A knowledge of analytical chemistry and of incompatibilities can be utilized, for a substance appearing as a precipitate is, of course, relatively insoluble.

GENERAL SOLUBILITY OF COMMUNLY USED SALTS IN WATER

I. Arranged by Acids.

Group A: Salts Mostly Soluble.

1. *Acetates and Nitrates:* all soluble (except bismuth subnitrate).
2. *Halogen group* (= iodides, bromides, and chlorides): Soluble except Ag; Hg (ous); Pb; Bi.
3. *Sulfates:* Soluble, except Pb, Sr, Ba; Ca sparingly soluble.
4. *Tartrates and Citrates:* mostly soluble.

Group B: Salts Mostly Insoluble.

1. *Arsenates*
Arsenites
Carbonates
Hydrates
(Ca sparingly soluble)
Oxides
Oxalates
Borates
Phosphates

} Insoluble, except those of alkali metals.

II. Arranged by Base.

The salts considered in this table are: Acetates (Ac), Halogens (H), Oxides (O), Sulfates (SO_4), Phosphates (PO_4), Oxalates (Ox), Carbonates (CO_3), Sulfides (S), Nitrates (NO_3), Citrates (Ci). Hydrates agree with oxides.

Those of the above salts which are *not mentioned* with the respective base are *insoluble.*

1. *Alkali Metals* (= Na, K, NH_4): all soluble.
2. *Lithium:* Soluble, except O and CO_3, sparingly soluble, and PO_4, insoluble.
3. *Mg, Al:* Soluble: NO_3, Ac, H, Ci, SO_4, S.
4. *Ca, Ba, Sr:* Soluble: NO_3, Ac, H, Ci, S; sparingly: O.
5. *Zn, Mn, Ni, Co, Fe, Hg(ic), Cu, Sn:* Soluble: NO_3, H, Ci, SO_4 (mercuric iodide is insoluble).
6. *Ag:* Soluble: NO_3, SO_4.
7. *Pb:* Soluble: NO_3, Ac.
8. *Bi, Sb:* Only soluble in form of double organic salts, *e. g.,* Bismuth and Ammonium Citrate, Antimony and Potassium Tartrate.
9. *Mercurous:* Insoluble.

Strength of Watery Solution.—The following table gives the amount of commonly used drugs which can be *safely prescribed in water enough to make 100 cc.* These should be memorized:

50 per cent, or grams: (= ʒiv in water q.s. ℥j) Tannin; Antipyrine; Acetate, Citrate, Salicylate, Iodide or Bromide of Potassium or Sodium; $AgNO_3$; $ZnSO_4$; Chloral; Cocaine Hydrochloride.

5 per cent, or grams: (= 25 grains in water q.s. ℥j) Alum; Phenol; Borax; $KClO_3$; $NaHCO_3$; $HgCl_2$; Tartar Emetic; Quinine Bisulfate; Citrated Caffeine; the majority of the soluble salts of alkalis, earths and metals.

Smaller quantities: 4 to 0.1 per cent: Boric Acid, 4; Morphine Sulfate, 4.5; Quinine Hydrochloride, 3; Quinine Sulfate, 0.13; Strychnine Sulfate, 2.

(It must be remembered that where several salts are prescribed in the same mixture, the solubility of each of these salts may be lowered.)

Solubility in Different Media.—As a general rule, *inorganic substances* are more soluble in water than in alcohol.

Basic alkaloids are insoluble in water, more soluble in alcohol.

Alkaloidal salts are soluble in either alcohol or water.

Gums are soluble in water, insoluble in alcohol. *Resins* and *essential oils* are the reverse.

(In making mixtures, it must be remembered that spirits, tinctures and fluidextracts all contain alcohol.)

Glycerin stands intermediate between alcohol and water as a solvent.

The following substances are much more soluble in glycerin than in water: Boric acid, alum, phenol, mercuric chloride.

Terms Used in Defining Solubility.—The following terms are employed in the U.S.P. to describe the approximate solubility, which is often sufficient for prescribing. Substances that are soluble in less than 1 part of solvent = very soluble. From 1 to 10 parts of solvent = freely soluble. From 10 to 30 parts of solvent = soluble. From 30 to 100 parts of solvent = sparingly soluble. From 100 to 1000 parts of solvent = slightly soluble. From 1000 to 10,000 parts of solvent = very slightly soluble. More than 10,000 parts of solvent = practically insoluble.

Official Solubilities.—The U.S.P. and B.P. state the solubility of articles as grams of substance to cubic centimeters of solvent; *i. e.*, a solubility of 1:10 means that 1 Gm. of substance requires 10 cc. of solvent for solution, at the standard room temperature, 25° C., 77° F., U.S.P.; 15.5° C., 60° F., B.P. The standards given in this book are those of the U.S.P. In percentage solutions, 10 per cent signifies that 100 cc. of solution contain 10 Gm. or cc. of the substance.— **Specific gravities** in the U.S.P. are taken at 25° C. unless otherwise stated (for instance, alcohol at 15.56° C.).

INCOMPATIBILITY

In the following compilation it has been attempted to arrange the incompatibilities into general groups. In this generalization it is not feasible to take account of individual exceptions. Care has been taken to err on the safe side. It is much more important for the physician to remember that mercuric chloride is generally incompatible with alkaloids than it is to know that it may be prescribed with some. In any case, if one is not certain that two substances will get along well together, it is safer to keep them apart.

Incompatibility is said to exist *when the constituents of a mixture interfere with one another in a way not intended by the prescriber.* If an interference is intentional, it is called an *intentional incompatibility.* If a chemical change occurs, the incompatibility is called *chemical.* When it consists in a precipitation of the substance by a change in the solvent, or when a chemic incompatibility does not interfere with the active substance, but produces an unsightly appearance, the incompatibility is *pharmaceutic.* If the interference is with the solubility, or if liquefaction or deliquescence occurs, the incompatibility is *mechanical* or *physical.* When without causing any chemic changes it interferes with the physiologic action of the ingredients, it is *therapeutic.*

Chemic incompatibility may result in explosion, precipitation, or the production of new substances with undesired properties. This is an application of the ordinary chemic reactions, and when the latter have been mastered, the subject is comparatively easy. *Substances used in testing for each other or that form antidotes are usually incompatible.*

Explosives.—Powerful oxidizing agents are liable to explode when mixed in concentrated form with easily oxidizable substances. *The most important oxidizing agents are:* chromic acid; concentrated nitric acid and nitrates; permanganates; chlorates; peroxides. *The most important oxidizable substances are:* all organic substances; sulfur, sulfides, sulfites and hyposulfites; iodine and iodides; phosphorus, phosphites and hypophosphites; reduced iron. Explosions may also result from mixing iodine with ammonia or turpentine; and chlorine with ammonium chloride. Explosions occur only when the substances are dry or at least concentrated, and when they are heated or percussed. *Dilute solutions* may be mixed without danger if not heated. Glycerin, phenol, and in some cases alcohol, behave like dry solids. Permanganate of potash or chromic acid or nitrate of silver decompose organic substances even in solution, but in this case without explosion.

Pills containing these easily decomposed substances are best made with inorganic excipient, clay and petroleum jelly.

Substances containing loosely combined oxygen may explode on concussion or heating when no reducing substances have been added; this is due to their containing dust or other organic matter. They should therefore be handled with care.

Gradual evolution of gas occurs especially on mixing acids with carbonates or sulfides; also when mixing strong acids with alcohols (= esters) or with chlorate (= Cl); also on mixing strong HCl and HNO_3. Formaldehyde effervesces copiously with oxidizing substances even in solution (hydrogen peroxide).

Incompatibility by Precipitation.—*Alkalis* precipitate earths, metals and alkaloids from their salts. Under alkalis may be included oxides, hydroxides, carbonates, phosphates, borates, arsenates and arsenites. *Chlorides, bromides and iodides* precipitate salts of Ag, Pb and some alkaloids. Iodide also precipitates mercuric salts, redissolving with an excess. *Sulfates* precipitate Pb, Ca and the other earthy metals, except Mg. *Salicylates, phenol and tannic acid* precipitate or color iron salts. Tannic acid also precipitates most other metals, alkaloids, and some glucosides and neutral principles. Salicylates precipitate quinine. *Salts of metals* are precipitated by alkalis, sulfides, tannic acid and proteins. They precipitate some alkaloids and acacia. *Mercuric salts* are often incompatible with other metals. *Silver and lead salts* are precipitated by chlorides, bromides and iodides. *Silver salts* are also incompatible with organic substances. *Iron salts* are colored by tannic acid, salicylate and phenol. *Calcium salts* are precipitated by alkalis, phosphates and sulfates; *magnesium salts* by alkalis and phosphates. *Alkaloid salts* and synthetic bases (antipyrine, etc.) are precipitated by alkalis, tannic acid, iodine, potassium-mercuric iodide, and some by iodides or metallic salts. *Acacia* is precipitated by alcohol, borax, Tr. Ferri Chlor.

Production of Substances with Undesired Qualities.—*Iodides* liberate iodine on the addition of acid and oxidizing agents, including H_2O_2, nitrites, salicylic acid, etc. They oxidize mercurous to the dangerous mercuric salts. *Chlorates* liberate chlorine with concentrated acids. *Chloral* liberates chloroform with alkalis. *Glucosides* (*f. i.* glycyrrhizin) are destroyed by acids.

Pharmaceutic Incompatibilities.—*Alcohol* should not be added to acacia, gelatin, proteins, emulsions, strong salt solutions. *Water* should not be added to alcoholic liquids in general (such as tinctures, spirits, fluidextracts, with some exceptions); or to ethereal liquids (oleoresins) or oils. Phenol should not be mixed with collodion. *Liquefaction* occurs when chloral is rubbed with camphor, menthol, phenol, salol, etc. Any of these, when rubbed together, or with coaltar antipyretics, are likely to liquefy.

Especially Incompatible Drugs.—The following are most likely to give incompatibilities, and combinations should therefore be scrutinized with special care: Acids, alkalis and carbonates; permanganates; iodides; salicylates; mercury, iron, silver and lead salts; tannic acid; alkaloids; methenamine.

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THE ADMINISTRATION OF DRUGS

The methods of administering drugs vary according to whether a strictly local action is desired, or whether it is aimed to have a drug distributed through the body, to secure "systemic effects." Local applications may have the object of protecting a surface or producing reflex effects; or they may be used as antiseptics or local stimulants; or for absorption and systemic actions.

METHODS USED CHIEFLY FOR SYSTEMIC EFFECTS

These require that the introduction or absorption of the drug should be sufficiently quantitative to insure definitely controllable effects. This condition may be met by the alimentary tract, and by injection under the skin, into the muscles, or directly into the circulation. Gaseous substances are administered by inhalation. Absorption and systemic effects may occur from other surfaces, mucous membranes, serous cavities, etc., which are utilized primarily mainly for local administration. They may then lead to toxic side actions

Oral administration is the most natural, the most ancient and still the most widely used method of administration. Its chief advantages are its convenience to the patient and its relative freedom of local damages. Irritant drugs do give rise, however, to disturbance of digestion, or even to gastritis, especially if they are taken in concentrated form, as in tablets. It can be minimized by giving them in such a form that they will not be rapidly dissolved in the stomach (pills), or by giving them at a time when the stomach is filled with food. Absorption is, of course, also delayed by these means. *Pills* should not be employed for insoluble powders or for corrosive drugs which require dilution.

Absorption from Alimentary Canal.—The absorbing power of the *stomach* is relatively low, even for water and soluble substances (Hirsch, 1892), so that the main absorption does not occur until the drug has reached the small intestines. The effects are therefore relatively slow and may be too slow for emergencies. The maximal concentration of soluble substances in the blood is generally reached in one-half to one and a half hours after their oral administration. The passage is quickest if the drug is taken when fasting and with water; somewhat slower with milk or soup; slowest after eating, especially when administered dry (Moritz, 1898). The conditions in the *small intestines* are favorable for absorption, which is aided by the long sojourn, the segmental movements, the extensive surface, the folds and villi. The *absorption of alkaloids* from the stomach is impeded by its acid reaction, and hastened as much as a hundred times by alkalinization. In the duodenum, they are well absorbed even with acid reaction, due partly to the presence of bile salts (J. Travell, 1938, 1940). Absorption from the intestines becomes progressively slowed if the solution remains in continuous contact (J. C. Andrews and Cornatzer, 1945).—Intestinal absorption (of galactose) is impaired in deficiency diseases such as pellagra, sprue, riboflavin deficiency and pernicious anemia (A. J. Beams, Free, and Glenn, 1942).

The Time of Administration.—Hypnotics and cathartics are most effective when their action coincides with the natural time of sleep and defecation, and if the external conditions are favorable. Stomachics are best given shortly before meals. If the drug is intended to act locally on the gastric mucosa, or if it is to be absorbed rapidly, it should be administered when the stomach is empty, half an hour or an hour before meals. Hot liquids favor absorption. Irritants are administered just after meals, when the stomach is protected by food. This is also the best time for securing slow and continuous systemic action. For intestinal action, the administration should be timed for the emptying of the stomach, two or three hours after the meal; this is also the best time for substances that cause offensive eructations.

Alterations of Drugs in the Alimentary Canal.—Some drugs (for instance, the antitoxins, insulin, epinephrine and arsphenamine) are destroyed so extensively in their passage through the intestines that oral administration is not sufficiently effective. Glucosides are partly destroyed, so that the oral dose must be larger. Drugs which require the action of the digestive juices for their solution (resins, oils, etc.) are more efficient by mouth than by other channels. The oral route must be used for drugs intended to act locally on the upper parts of the digestive tract. Absorbable drugs are apt to act on the intestine more powerfully when they are administered by vein than when they are taken by mouth (Uhlmann and Zwick, 1920).

Sublingual Absorption.—The under side of the tongue absorbs quite well and avoids destruction by digestion and the liver. "Hypodermic" or other friable tablets may be held under the tongue, swallowing being avoided until the taste of the drug has disappeared. Liquids may be dropped on a pellet of cotton (W. Paulson, 1916). The method is valuable for glyceryl trinitrate. The steroid sex hormones are absorbed materially better than when swallowed. In general, the sublingual absorption parallels the oil:water solubility coefficient; but alkaloidal salts are not absorbed materially better than the free alkaloids (R. P. Walton, 1944). The sublingual route is not sufficiently effective for alkaloids to offset the objectionable taste (Walton and Lacey, 1935).

Rectal Administration.—The stomach and small intestine may be avoided by giving the drugs per rectum, either in the form of enema or suppositories. The rectum and colon absorb many soluble substances; and the effects are often greater or more prompt than with oral administration (for alkaloids, salts, narcotics, etc.; and for sodium salicylate or iodide, chloral, methylene blue, atropine and morphine, Enesco *et al.*, 1939).

Enemas for the absorption of the medicine should be as small as possible, but not so strong as to produce local irritant effects. One or 2 ounces is usually the proper quantity, the rectum being first cleansed with warm water. When enemas are employed for their mechanical effect, the amount must be 1 or 2 pints. These should be raised to the body temperature. Rectal injections, after they have passed the internal sphincter, spread quite rapidly through the whole *colon*, where absorption chiefly occurs. Observations on colostomized patients show absorption of glucose, sucrose, methylene blue, atropine, neoarsphenamine. The colon does not excrete methylene blue, glucose or sucrose (Curry and Bargen, 1935). *Rectal absorption* is materially increased by the injection of ether or alcohol (Albi and Boyd, 1931).

Subcutaneous or Hypodermic Administration.—The injection of solutions through a hollow needle into the loose subcutaneous tissue has the advantage of securing quicker and more certain effects, and more exact dosage. Their absorption occurs chiefly through the capillaries and only slightly by the lymphatics. Hypodermic injections are generally made into the forearm, arm, thigh or nates. For bulky injections, *e. g.*, for antitoxin or for saline solution, the loose areolar tissue of the subscapular or mammary region is chosen. The subcutaneous dose may often be made somewhat smaller than the oral dose. The *rapidity of absorption* from hypodermic injections may be hastened by massage, by distributing the injection over several places, and by dissolving the drug in a *small* amount of fluid. The total concentration in salts should not exceed that of the blood, or the injection will be painful. Normal saline solution is the least irritant solvent for alkaloids. *Alkalinization* promotes the absorption of alkaloids (J. Travell, 1940). The absorption of histamine and other drugs (penicillin) may be greatly slowed by injecting them in a *beeswax and mineral oil* mixture, so that the effects of a single dose may last for days (C. F. Code and Varco, 1940). Subcutaneous injection is inadmissible if *local* effects in other parts of the body are desired (*e. g.*, for stomachics, cathartics, locally acting emetics, etc.). *Edematous areas* absorb poorly. The hypodermic injection of drugs that are not local irritants produces little discomfort and no after-effects, provided that reasonable asepsis is preserved. *Irritant drugs* cause severe pain and may be followed by induration, sloughing and abscess. This holds true also of oils, especially mineral oils (Budai, 1922). Hypodermic injection was probably first practiced by E. Rynd, 1844, but was introduced practically by Alex. W. Wood in 1853. Pravaz invented his syringe in 1853 for the injection of aneurisms (Macht, 1916).

Intramuscular injections are made by thrusting the needle through the skin deep into the substance of the gluteal or lumbar muscles, where the fluid spreads out between the fibers and along the fasciae, giving a large absorbing surface relatively poor in sensory nerves, so that absorption is more rapid and pain less than when injections are made into the subcutaneous areolar tissue. There is also less chance of abscess formation (Claude Bernard, "Les Anésthesiques," p. 70; Meltzer and Auer, 1904). Watery solutions spread rapidly during injection; oily and viscid fluids first form a globule, with local trauma of the muscle, and then spread slowly for five or ten minutes along the fasciae. After this time there is little further spreading (W. F. von Oettingen, Todd and Sollmann, 1927). The spreading is much more extensive for solutions than for viscid suspensions (L. W. Shaffer, 1929). Relatively insoluble powders suspended in oil may be injected intramuscularly to establish a depot for the gradual absorption and continued action of a drug, such as bismuth or mercury salicylate in the treatment of syphilis. If the injected material is irritant, directly or by solution in the lymph, there may be considerable local necrosis. Insoluble material that is not absorbed becomes encapsulated. Mineral oils must not be injected under the skin, as they are not absorbed and give rise to tumors.

Fatty oils when injected intramuscularly into rats become encapsulated in a few days, forming oil cysts which may remain for some months and which often form abscesses, especially with almond oil. With hypodermic injections, the oil globules generally disappear without cyst or abscess formation (Emery and Matthews, 1943).

For *ambulatory* patients, intramuscular injections are usually made into the gluteal muscles, through a 2 to 2½ inch needle inserted near the center of the buttocks, somewhat toward the upper and outer quadrant, to avoid striking the bones or the sciatic nerve. It is important to make certain that the needle is not in a vein. Auer and Meltzer, 1911, advised the sacrospinal muscles in preference to the gluteal, as giving better absorption with less pain and other complications.

Intraperitoneal and intrapleural injections are employed in experimental technic, and resemble subcutaneous injections, the drug being absorbed more rapidly. Intraperitoneal injection was introduced clinically by Schmidt and Meyer (1905). It has a distinct field, especially for the administration of saline or dextrose to infants who offer difficulties for intravenous injection (Aikman, 1920; H. M. Sanford and Heitmeyer, 1928). Irritants should not be used, but neoarsphenamine may be employed. Oil is absorbed slowly (E. W. Schwartze, 1921). The *pleura* absorbs through the parietal and pulmonary surface, but the absorption is less than from the peritoneum (Naegeli, 1913). In both membranes, it occurs by the blood rather than lymph. Gravity plays a part, the absorption being rather better with pelvis-down position (Dandy and Rowntree, 1914). Waddell, 1923, utilized *intrahepatic injections* in place of intravenous injections, for small laboratory animals, *i. e.*, frogs, turtles and rats.

Intravenous Injection.—The injection of aqueous solutions into the blood stream is necessary with a few substances for which other methods are not available; for instance, those that are decomposed in the digestive tract, and those that are not satisfactorily absorbed or that produce irritation from the subcutaneous tissues. Arsphenamine is the most important example. Intravenous administration may also be used in emergencies, to secure immediate action. Aside from such definite indications, intravenous injections should be avoided, for they imply a greater risk to the patient than do the other methods of administration, since injection of a foreign substance into the blood stream alters the equilibrium of its colloids, and this may result in alarming fall of blood pressure and even fatal reactions. These have been called "*speed shock*" (S. Hirschfeld, Hyman and Wanger, 1931), because they are more frequent and more serious if the injection is made rapidly. Slowness of injection reduces the liability of reactions. Substances that are definitely incompatible with blood, such as acids or metallic salts, are especially dangerous; but almost all substances may apparently produce reactions in some individuals, under conditions that are not understood and cannot be foretold (Hanzlik and Karsner, 1920; Hanzlik, de Eds and Tainter, 1925; see index, "Allergic Reactions"). The circulatory congestion arising from rapid injection has been studied in dogs by Yeomans, Porter and Swank, 1943. If the distilled water has been allowed to stand it is likely to become contaminated with pyrogenic spores, causing *febrile reactions*. *Irritant substances* may produce thrombosis, inflammation and fibrosis of the vein; but this results more commonly if irritants escape into the perivascular tissue. Aside from the temporary discomfort, this renders the vein unsuitable for further injections. This may be a serious matter later, should a real occasion for intravenous therapy arise. With many substances accidents are so rare that there should be no hesitation in giving these intravenously, if an emergency demands the immediate effect of the drug, or if the drug can not be given effectively by the less risky channels; but unless special indications such as these do exist, intravenous therapy is not advisable. *Intravenous injections of oil* result in pulmonary embolism, even if the droplets are emulsified so as to be smaller than erythrocytes (Markowitz and Mann, 1930). Injections of air may also be dangerous. Intravenous injections are usually made into the veins of the arm. Varicose veins may be used if others are not available, but are more liable to thrombosis.

Instantaneous action is an important advantage only in emergencies; otherwise it is generally undesirable, especially if continued rather than acute effects are desired. The concentration of the drug during the injection rises materially above the level of the continuous dosage, and may result in brief but stormy reactions that differ in kind as well as in degree from the ordinary actions of the drug. The "primary fall of blood pressure" that is liable to occur with all kinds of intravenous injections has always been an annoying complication to experimenters on animals; it is no less serious in clinical practice. The claim of *exact dosage* is somewhat misleading. Intravenous injection controls the quantity of drug introduced, but exact dosage really means the exact adjustment of the quantity to the desired effect. This may be more difficult with intravenous than with oral administration; for with the latter the physician can begin with a relatively small dose, and add further doses, according to the response of the individual patient. With intravenous injection, such frequent repetitions are usually not practicable, and consequently the dosage is often too large or too small. *Avoidance of gastro-intestinal irritation* is also a rather misleading claim; for the most difficult element of these disturbances is often central, and in that case (for instance, with digitalis) the nausea and emesis are not diminished by intravenous injection. The strictly local irritation can often be avoided by suitable methods of oral administration, for instance, free dilution with water or food, etc. *Intra-arterial injection* is generally less potent than intravenous, as part of the drug is absorbed by the peripheral tissues. The difference is especially marked for epinephrine (Ehrismann, 1928).

Historical.—Intravenous injection was tried rather extensively in the seventeenth century. Claude Bernard (Les Anesthésiques) described it as the ideal method for animals, but considered that it would never become practical and common in clinical medicine. The modern application dates from Landerer, 1881, and F. Mendel, 1908 (history, Epstein, 1915; Macht, 1916; Eggleston, 1917).

Intracardiac injection is used in animals for systemic effects, but clinically exclusively for the resuscitation of the heart by epinephrine (E. Vogt, 1914). The injection is usually made into the ventricle through a 4-inch needle inserted in the 4th intercostal space at the left margin of the sternum. A. S. Hyman, 1930, prefers to inject into the right auricle. The puncture itself probably plays an important part in the stimulation. **Intrapericardial Injections.**—Solutions are quite rapidly absorbed from the pericardial sac into the heart muscle. Gunn and Martin, 1915, suggest that this could be utilized in epinephrine resuscitation. The human *pericardial cavity* permits ready absorption of phenolsulfonephthalein through the subepicardial capillaries: the large molecules of vital red are not absorbed (H. J. Stewart *et al.*, 1938).

Intra-osseous injection by way of the bone marrow, through a needle thrust into the sternum of adults, or the upper third of the tibia or lower third of the femur in children, amounts practically to intravenous injection, reaching the general circulation almost immediately. It can be used when the veins are not accessible (L. M. Tocantins, 1940). Since it may lead to pulmonary embolism (Wile and Schamberg, 1942) it requires experience and is safe only if the technic is good (Tocantins and O'Neill, 1945).

Inhalation is used only for gaseous medicines, such as anesthetics or oxygen. The effects do not depend upon the quantity given, but on the concentration of the gas and the time during which it is administered. The rich capillary area of the alveoli (which in man covers nearly a thousand square feet, 90 square meters; Zuntz) is one of the best absorbing surfaces, so that the action is very rapid. The lungs also absorb fluids and dissolved substances rapidly, if these are introduced through the trachea.

The absorption of fluid from the lungs far surpasses ordinary conceptions: Semmola states that Gobier poured about 30 liters of water into the trachea of a horse. Instead of killing the animal, the water was absorbed. Colin ran a *continuous* stream of warm water into the trachea of a horse, at the rate of six liters per hour: This eventually killed the animal by direct water injury of the lungs and tissues, but no trace of the water was found in the lungs. Dogs received 200 cc., rabbits 30 to 40 cc. of fluid into the trachea without damage. Similar observations are described by Winternitz. One accidental experiment on man was recorded by Bichat. A stomach tube was inadvertently introduced into the trachea, and through it bouillon was poured into the lung and absorbed "without disturbance." If the fluid is injected much more rapidly than it can be absorbed, it will, of course, produce asphyxiation.

Absorption of dissolved substance from the lungs is also rapid. If ferrocyanide in solution is injected into the trachea, it can be demonstrated in the carotid blood in two minutes. Claude Bernard showed that opium alkaloids are much more active by trachea than when injected hypodermically, and suggested clinical utilization of this channel (by piercing the trachea with a hypodermic needle) when the circulation is too low for absorption from other situations.

Absorption of chemotherapeutic substances from inhalation of nebulized sprays was studied by N. Mutch, 1944.

METHODS USED CHIEFLY FOR LOCAL EFFECTS

Practically any method of administration may be utilized either for local or systemic actions, according to circumstances. For instance, subcutaneous injections are used for local anesthesia, and intravenous injections for sclerosing varicose veins.

Intracutaneous (*endermic, intradermal*) *injections*, into the corium (F. W. Taylor, 1938) of the skin (instead of under the skin) are used to provoke local diagnostic skin reactions and for local "infiltration anesthesia." The distance from the blood vessels makes the absorption slower than with hypodermic injections (F. Luithlen, 1926). It is sufficient, however, to produce marked systemic reactions, *e. g.*, to epinephrine. Even solid elements may be gradually absorbed (Kasahara, 1916).

Injections into the Central Nervous System.—*Subarachnoid injections* (subdural, intraspinal, lumbar) are used to secure direct action on the spinal cord or nerve roots, especially for spinal anesthesia, and for colloidal drugs that do not readily penetrate the nervous substance from the blood, such as tetanus antitoxin; and for iodized oil in roentgenography. The technic is that of lumbar puncture, some cerebrospinal fluid being withdrawn before the injection is made. There is often some spinal irritation and the procedure may be dangerous, especially if the poison produces local effects or is conveyed directly to the medulla. The action of drugs on the central nervous system is generally more pronounced if injected into the cerebrospinal fluid, for they penetrate the nervous tissue much more readily from this direction than from the circulation (U. Friedemann, 1942). For instance Lewandowsky, 1900, found that strychnine is ten times as potent when injected intraspinally as when injected intravenously.

The efficiency of the absorption of drugs from subdural injections into the general circulation is in dispute. Becht, 1920, found no systemic effects after subdural injection of epinephrine, nicotine and secretin. He attributes the contrary results of Meltzer and others to direct entrance into veins. The absorption may be modified by inflammation of the meninges (*f. i.*, increased, Carnier, 1916; diminished, Meheteus and West, 1917; unaltered, Stollmann and Swift, 1915). The irritation of arsenicals and mercurials may be somewhat diminished by mixing them with serum. *Subarachnoid irrigation* has been tried experimentally (Weed and Wegeforth, 1919). Normal saline produced toxic effects, but Ringer's solution appeared harmless and prolonged the life of animals with meningeal infection. The spinal cord is especially sensitive to changes of *p*H (Dandy and Blackfan, 1913).

Intracisternal and intracerebral injections have been used experimentally. The injections are at once conveyed to the ventricles and produce local and mechanical effects often different from the systemic action of the drug.

Intraneural injections are used chiefly for direct destruction of the nerve, by alcohol, etc. It has been claimed that solutions injected into peripheral nerve trunks ascend rapidly along their lymph channels into the central nervous system (Hoester and Whitman, 1931); but this has been disputed.

Application to the skin is practiced in the form of ointments and plasters, especially for prolonged contact; liniments, especially for reflex stimulation; watery or alcoholic solutions, watery "washes" or moist dressings, especially for antiseptics; dusting powders; poultices, etc. They are generally intended for local actions, as absorption from the skin is poor and uncertain. It is not negligible, however, and systemic effects sometimes arise when they are not desired. The most important use of the skin for systemic therapy is in mercurial inunction. In this case the ointment is vigorously rubbed into the skin, so as to press the liquid mercury into the hair follicles and gland ducts, where it is gradually changed into absorbable compounds. The lower layers of the skin absorb readily, but the stratum corneum is only slightly permeable to most substances. *Skin absorption* is therefore greater where the epidermis is thin, in the axilla, loins and the inner surface of the arms and thighs. The permeability increases if the epidermis is saturated with water by perspiration, or by occlusive dressings, or alkalis or hydrosulfides. Increased vascularity of the skin favors absorption by carrying away the absorbed drug and thus maintaining a steeper concentration gradient. This would result from active or passive hyperemia, heat, friction, any form of irritation, or massage. Absorption is also increased by keratolytic agents—acetic or salicylic acid, pyrogallol, resorcin—which dissolve the epidermis. It is decreased by astringents, such as tannic acid or formaldehyde (Milbradt, 1933). Oils and ointments delay the absorption of fat-soluble substances, such as phenol, mustard oil or dichlordiethylsulfide, analogous to the partition of a substance between good and poor solvents in a test tube (Sollmann, 1918). The influence of the ointment base differs, therefore, according to the substance (Sauerland, 1912). *The absorbability of different substances* depends on their physico-chemical properties rather than on their chemical constitution. Absorbable substances must be freely soluble in *both* oil and water. Volatility is a favoring factor, by facilitating penetration into the skin glands. Many gases are absorbed quite freely. Low melting point is favorable (Lazarew, 1932). Methods for studying systemic poisoning by absorption through the skin are described by Draize and Lang, 1944. Skin permeability is reviewed by H. O. Calvery *et al.*, 1946.

Baths are used almost exclusively for local and reflex effects. For calculating concentrations, the volume is taken as 200 liters for adults, 50 to 100 liters for children.

Wounds and Ulcers.—Removal of the epidermis facilitates penetration and absorption if the circulation is good, as in recently abraded surfaces, blisters, burns, etc. In older burns and ulcers, the circulation becomes restricted and absorption is poor.

The dental pulp readily absorbs water-soluble and diffusible substances, including alkaloidal salts, but not colloidal solutions, such as snake venoms and insulin; nor epinephrine (Obiglio, 1930).

Applications to Mucous Membranes.—Drugs, especially protectives (demulcents), astringents and antiseptics, may be applied to the mucous membranes for local effects on the surface or for superficial penetration. Radiopaque substances may be applied for Roentgen diagnosis. Mucosae are more or less effective absorbing surfaces (Macht, 1917, 1923) so that systemic actions may develop, and they may be utilized for this purpose. The rapidity of absorption differs considerably; for instance, the urinary bladder absorbs poorly, the urethra very freely. Pathologic changes in the mucous membrane, as by scalding or freezing, impede absorption (Macht, 1933). Mucosae are generally rather sensitive to local irritants, especially the conjunctiva and urethra, so that locally acting drugs are used on these in about a fourth to half the concentration that would be employed on the nasal mucosa; the mouth and vagina are less sensitive and may be treated generally with twice the nasal concentration.

Methods of Application.—Medicines are applied to the mucous membranes by irrigation or by painting; to the respiratory tract by spraying and inhalation.

Irrigation serves chiefly for cleansing and for application of heat, but medicinal agents are often added, especially mild alkalis, sodium bicarbonate or sodium borate for cleansing; or mild astringents and antiseptics, such as boric acid, potassium permanganate, colloidal silver or organic mercury compounds. The time of contact is so short that real antisepsis cannot be expected. This is slight even when some of the solution is left in place, as in the urinary bladder or the nasal sinuses. *Painting* or swabbing permits more prolonged contact with stronger solutions; and this may be further extended by the use of tampons, generally with glycerol, sometimes with mucilaginous media. Iodine and silver nitrate are used in this manner to produce astringency, irritation and cauterization. The antiseptic action of these and of germicidal dyes is confined to the surface and debris, because living cells resist the penetration of effective concentrations.

Vehicles.—Surfaces that do not normally come into contact with water are generally irritated by it through osmosis. This is avoided by isotonic solutions, *f. i.*, 0.85 per cent sodium chloride. Solutions in oil are also used to avoid osmotic irritation. Their immiscibility with the moisture of the mucosae prevents direct contact with the cells, and their action is therefore slower and more prolonged. Ointments make even poorer contact, because viscosity limits their spread.

Conjunctiva.—Solutions are dropped into the conjunctival sac to act on its mucosa, and on the iris and ciliary body. Absorption occurs freely from watery solutions (more slowly from oily solutions) by the mucosa and also by the lachrymal ducts, so that the systemic effects often follow the application of drugs, atropine to the eyes, for instance.

few milligrams of apomorphine applied to the conjunctiva of a dog suffice to produce vomiting (Macht, 1917). The corneal epithelium is permeable to acid dyes, much less so to basic dyes. This channel also avoids the destructive action of the digestive tract and liver. Insulin, *f. i.*, is effective, requiring only 60 per cent more than by hypodermic injection, in rabbits. The commercial solution is not irritant (C. D. Christie and Hanzal, 1931). *Excised cornea and sclera* are not permeable to purely water-soluble or purely fat-soluble substances, but only to those that are soluble in both (D. G. Cogan *et al.*, 1944).

Isotonicity is important for the application of solutions to the conjunctiva. Hypotonic solutions tend to render the cornea turbid. Sufficient approximation is attained with: NaCl, 0.8 per cent (2 level teaspoonfuls to the quart or liter), or boric acid or sodium bicarbonate, 2 per cent (4 teaspoons to the quart), or sodium borate, 2.5 per cent (6 teaspoons to the quart). The pH is also important; 8 is optimal; irritation occurs above 9 and below 6.6.

The *mouth, pharynx and glottis* may be treated by troches, by swabbing, or by mouth washes, gargling or irrigation. It is doubtful whether gargling generally reaches the glottis or indeed the posterior pharynx, unless a careful technic is followed (Swain, 1936). Antiseptics would not be in contact sufficiently long to be effective. They merely wash away living and dead bacteria from the surface, as does water.

Nasal applications may be made by dropping saline or oily solutions into the nostrils, by irrigation or sprays, or by swabbing. The nasal mucosa is sensitive to hypotonic and astringent solutions, less so to hypertonic. Absorption occurs rather easily, so that the effects of pituitary, insulin and allergic agents may be produced. Nasal injections of local anesthetics have often caused serious poisoning. The nasal mucosa is a natural channel for securing immune reactions and has been used to this end.

It was the original Chinese method of inoculating against smallpox, and was introduced into England by Richard Mead ("The Gold-headed Cane"). Injection under the mucous membrane of the nasal septum gives extremely rapid absorption, the efficiency approaching intravenous injection (Pilcher, 1914, 1915). The mucosa of the frontal sinus absorbs rather poorly in animals (J. H. Childrey and Essex, 1931).

Cumulative pulmonary irritation by oil aspirated from nose drops occurs especially in young children, leading to characteristic changes and sometimes to pneumonia (Pierson, 1932).

Sprays and inhalations are used in the respiratory tract, from the nose to the alveoli. The latter, however, are reached directly only by gases. Substances that can be vaporized by heating may be evaporated with boiling water, *f. i.*, volatile oils, inhaling the steam through a funnel or cone; or by the "steam-atomizer"; the steam does not penetrate far into the bronchial branches, but as it cools, it condenses on the mucous membrane of the larger bronchi (Semmola). This establishes surface depots of the substance, which saturate the air stream and thus reach the deeper passages in more dilute form. Roentgenography has shown that the churning of the respiratory movements spreads the fluids extensively, giving wider direct contact and larger surface for evaporation. Incidentally, the heat and moisture furnished by steam are often beneficial, perhaps more so than the drugs which it carries. To reach the lower air passages, the steam should be inhaled deeply with the nostrils closed, the mouth wide open, and the tongue protruded. *Inhalation of smoke* is also sometimes utilized. In this, the substance exists partly in very fine suspension, as a mist, which does not condense on cooling as does steam. *Dust* is not carried farther than the ciliated epithelium extends, unless it is suspended in fluid (Barclay *et al.*, 1938). Particles larger than 12 microns cannot enter the alveoli; this is the maximal size found in miners (Policard). *Sprays* secure coarser suspensions mechanically. These behave like the steams, but are generally not inhaled as deeply, and lack the heat of the steam. They are used mainly for effects on the nose, pharynx, larynx and trachea.

Intratracheal Injections.—Small quantities, 2 or 3 cc., of oily solutions may be injected directly into the trachea, usually through the glottis, after local anesthesia. They are then distributed by respiration, like the sprays and steams (Balvay, 1921; J. A. Thompson, 1897; A. Ochsner, 1932). Iodized oil is thus used in roentgen diagnosis.

The *vagina* absorbs freely, and clinical poisoning by this channel is frequent, especially in connection with the improper use of mercuric chloride douches (Macht, 1918, references; G. D. Robinson, 1927). The *uterine cavity* is also an absorbing surface (iodine, Higuchi, 1908).

The *urethra* in man holds 4 to 15 cc. of fluid when distended, and absorbs readily, so that poisoning has frequently occurred from the excessive application of local anesthetics.

The absorption of local anesthetics from the urethra was studied by Sollmann, 1918. The rapidity of absorption is illustrated by the injection of 1 per cent apomorphine into the urethra of a male dog; vomiting occurs in three to five minutes (Macht, 1918).

The mucosa of the *prepuce* is also a good absorbing surface.

The *urinary bladder* absorbs poorly. Strychnine, apomorphine and morphine are almost harmless when injected into the bladder, if the urethra has been tied (Macht, 1918). The reaction plays a considerable role; the absorption of nicotine is much greater at *p*H 9 than at 5 (J. Travell). Even salts and water are absorbed poorly, but urea is somewhat absorbed.

If the ureters and urethra of anesthetized dogs are ligated and the bladder is filled with water or with isotonic sodium chloride solution, the volume remains practically unchanged for hours. Hypertonic sodium chloride produces injury and bleeding. With 10 to 30 per cent urea, about a tenth is absorbed in two hours, and no more in fourteen hours. Mixed solutions lose in urea and not in sodium chloride (Conradt, 1937).

The *ureter, and renal pelvis* absorb fairly well (Macht, 1918); and there is the additional possibility of injecting into the circulation through the pyelovenous backflow (see under Iodized Oils).

CONDITIONS INFLUENCING ABSORPTION

The time required for absorption into the body and into the cells ranges from a few seconds (*e. g.*, hydrocyanic acid) to several weeks (*e. g.*, lead). The rapidity of absorption depends upon the nature of the drug, the place of administration and other factors. The place of administration has been discussed in the preceding section.

Solubility.—Only soluble drugs can be absorbed (except the small quantities taken up by phagocytosis); but the solubility in the protein-containing fluids of the body is not necessarily the same as the solubility in water. The solubility may also be modified by chemical changes produced by the digestive or tissue juices.

There is considerable uncertainty in the absorption of *solid particles* even when they are soluble. They should therefore be avoided unless a very slow action is desired. They are practically unabsorbable from the alimentary tract, although Koellicker and many others, on feeding rabbits with carbon, found particles in the prevertebral and mesenteric ganglia.

Influence of Colloids.—Oil, gums, extractives, kaolin and colloids generally hinder absorption, partly by adsorption of the drug, partly by impeding its access to the absorbing surface. Food in the alimentary canal has this action. The isolated active constituents (alkaloids, etc.) are preferred if a quick systemic action is desired, while the galenic preparations (extracts, tinctures, pills, etc.) are used for local effect. Oils, especially mineral oil, delay the absorption of oil-soluble principles, such as carotene; bile hastens their absorption by emulsification; so does saponin, unless it causes irritation. Alcohol also favors their absorption.

Even with isolated cells there is usually a layer of undisturbed fluid on the surface of the cell, although the fluid is violently stirred (the "*Noyes-Whitney layer*"), and this is exaggerated by the viscosity of colloids. The frog heart, because of its spongy character, has relatively rapid intercellular penetration so that it responds to drugs in a few seconds.

Fullers' Earth (hydrous aluminum silicate) has a high adsorbing power, especially for alkaloids, varying in degree with different samples (Lloyd, 1916). McGuigan, 1914, found that this renders strychnine insoluble in acid fluids, so that the bitter taste develops quite slowly; and that it delays and diminishes the tetanic action in frogs. Fantus, 1915, showed that the combination is not dissolved in the stomach, but dissociates gradually in the intestines. He found the suitability of the earth as alkaloidal antidote very limited. Clowes and Walters, 1920, claim that the fullers' earth adsorbate is not broken up by sodium bicarbonate, as assumed by the other authors; but that this requires the presence of soap or other unnamed constituents of protoplasm. Sollmann found that bile salts, whose general properties resemble those of soaps, do not liberate demonstrable quantities of emetine. Sabbatani, 1913, found considerable antagonism between strychnine and *colloidal carbon* when mixed *in vitro*. The intravenous injection of the carbon furnished some protection against the oral administration of strychnine; but this was too uncertain for practical application. Von Paulucci, 1915, showed that fatty substances (including petrolatum) diminish the toxicity of strychnine, both hypodermically and with direct application to the nerve centers.

Concentration.—Absorption varies generally in the same direction as the concentration, especially for hypodermic injections; but the relation is not simple. Absorption tends to increase with the *extent of absorbing surface* (*e. g.*, by making multiple hypodermic injections). This seems to be less important in the intestines.

Changes of the Absorbing Cell.—In the alimentary canal, injury to the absorbing cell may either facilitate or hinder absorption; astringents tend to have the latter effect, corrosives and simple irritants the former. Sollmann and Hanzlik, 1911–1913, found that phenol, alcohol, iodide and probably other substances tend to inhibit their own absorption; so that the absorption, at first rapid, is promptly slowed.

Circulation.—The rapidity of absorption is proportional to the rapidity with which the drug is removed (just as a burning lamp-wick absorbs the oil more quickly; Mialhe). It therefore increases with the rapidity of the circulation and of the lymph flow. Active hyperemia (hot air; Klapp, 1901) and hemorrhage hasten absorption; while it is delayed by venous stasis, passive congestion, deficient heart action, vasoconstriction, catarrh, etc. Increase of lymph flow, by moderate *distention* and *massage*, quickens absorption. Excessive distention diminishes absorption by slowing the local lymph flow (Hamburger, 1907).

Severe hemorrhage (15 to 25 cc. per Kg.) increases the susceptibility of cats to physostigmine, chloral, ouabain and strychnine. Normal susceptibility returns in three-quarters to two hours, parallel with the restoration of the blood volume. The mechanism is not clear (H. Gold, 1927).

The absorption of gases from intact intestines is arrested by ligation of the arterial supply, and diminished by lowering the blood pressure and by shock; by tying the portal vein, by raising intra-abdominal pressure, and by applying solutions of tannic acid, alum or acacia to the mucosa (Admiraal, 1943).

Absorption by Blood and Lymph.—Most soluble substances are absorbed from the alimentary canal by the blood, rather than the lymph. This also holds for the serous cavities; methylene blue injected into the peritoneum or pleura, for instance, appears in the urine before it is seen in the thoracic duct (Starling and Tubby). A few drugs, however, take the lymphatic path. Tetanus and diphtheria toxin, and perhaps other toxins, are absorbed from the local injections by the nerve sheaths, and reach the central nervous system along these (Meyer and Ransom, 1903; Meyer, 1915).

Absorption in Absence of Circulation.—Considerable absorption occurs when the circulation has stopped. Thus, strychnine and morphine are absorbed by frogs with ligated hearts, producing interesting modifications in their actions (Meltzer, 1911–1913). Abel, 1912, and Abel and Turner, 1914, believed that the solutions in cardiectomized frogs are circulated by the lymph hearts; but Meltzer, 1914, Joseph, 1914, and Githens and Meltzer, 1915, affirm that general effects from the local injection of strychnine, fuchsin or epinephrine may develop when all the lymph hearts are definitely excluded, the absorption occurring through the lymph spaces. The absorption in frogs is delayed by destruction of the spinal cord (Filippi, 1912). *Considerable absorption occurs also in dead animals* (Sollmann and Hanzlik, 1913), probably by diffusion.

Sojourn in the Blood.—The passage of absorbed or injected substances from the blood into the tissue is a very rapid process for diffusible substances, materially slower for colloids.

Masoin (1903) found the time which elapses before just toxic doses disappear practically completely from the blood, after intravenous injection, to be for arsenic, nine-tenths to thirty seconds; cyanides, two to six minutes; diphtheria toxin, four minutes; antitoxin, several hours. *The sojourn of dyes in blood stream* has been investigated in the development of methods for measuring the blood volume. One group remains in the plasma for long periods; another group is excreted rapidly by the urine; a third group disappears from the plasma, but is not excreted by the kidneys. These groups have no apparent relation to the chemical structure (Dawson *et al.*, 1920). In general the capillaries are *more permeable to electronegative* than to electropositive substances. This explains the greater toxicity of basic drugs, and the rapid action of cobra venom in contrast to the slow action of most toxins, which therefore have a longer "incubation" period (U. Friedemann, 1942).

Distribution of Drugs within the Body.—Drugs are not distributed uniformly, but tend to pass first from the blood into the fluid bathing the tissues, and may accumulate especially in certain cells, according to their permeability and physical and chemical affinities. This influences their action; either by bringing them in contact with reactive tissues, or by storing them in places where they may be inactive. The distribution has been studied in relatively few cases, especially for inorganic poisons. It appears to be altered by disease; *e. g.*, degenerating tissue takes up more iodide, etc. The major quantity of dissolved substances is generally found in the skin, liver and muscle because of their great mass. If insoluble compounds are formed, these are laid down chiefly in the kidneys and liver. If colloids, and especially flocculates, are injected by vein, they are largely sifted out in the capillaries of the lungs, liver and spleen, chiefly by the phagocytic *reticulo-endothelial cells* (review, B. Sacks, 1926).

The chlorides, bromides and related ions accumulate in the extracellular fluid of all organs, but mainly in the skin and blood. The thyroid stores a relatively high percentage of iodine as thyroxin. The bones retain the earthy metals and fluoride. The heavy metals are deposited as loose organic compounds, especially in the kidneys, liver and spleen; mercury as a loose globulin compound; arsenic as a more stable nuclein combination (Vamossy, 1905). Iron deposits serve as a reserve stock of this metal.

The "blood: brain barrier" which controls the diffusion of substances from the blood into the central nervous system differs altogether from the passage between the blood into the cerebrospinal fluid or from this into the brain (U. Friedemann, 1942, review), for intravenous injection of almost all basic aniline dyes stains the brain without staining the cerebrospinal fluid. Acid dyes do not stain the brain (P. Ehrlich, 1887). The brain capillaries are therefore directly permeable to basic dyes and not to acid dyes. They are also permeable to lipid solvents (ethyl urethane, ethyl alcohol, paraldehyde), to alkaloids and sulfonamides; less permeable to iodide, bromide and thiocyanate ions than to chloride ions; impermeable to ferrocyanide, neoarsphenamine, germanin and trypan blue. They are permeable to proteins and antibodies, probably impermeable to viruses. The molecular size is relatively unimportant, and so is lipid solubility for basic dyes. Negative electric charge is probably more important. Epinephrine materially increases the permeability of the cerebral capillaries to the substances for which they are naturally permeable, but does not change it for impermeable substances (Friedemann and Elkeles, 1932).

Chemic Changes in Drugs.—Many poisons are altered in the body, and generally rendered less harmful, by oxidation, reduction, hydration or dehydration, or other decomposition, or by the storage of the poison in certain organs, or by its combination with other substances which render it harmless. Were it not for the power of the body to destroy or remove poisons, and thereby to recover from their action, all therapeutic use of drugs would be impossible. This disintoxication makes it necessary to administer the drugs progressively in order to maintain their effect; it may require the use of continuously increasing doses as the power of disintoxication becomes more developed. On the other hand, the alteration of the drug may result in a more toxic substance, as in the case of the nitriles; or may render it more effective therapeutically as with arsphenamine.

Decomposition by Digestion.—The digestive juices destroy some organic poisons by hydrolytic cleavage, especially the proteins, toxins and antitoxins, and the glucosides. On the other hand, they are necessary to saponify and liberate the active constituents of insoluble esters, *e. g.*, phenyl salicylate. The acidity of the gastric juice is important for the solution of bases. It often splits off acyl groups.

Decomposition in Tissues.—Feeding with *thyroid* diminishes the toxicity of acetonitrile, by preventing its conversion into cyanide (Reid Hunt, 1905). Organic compounds of metals (cacodyl, etc.) only develop the metal action after oxidation. Many organic acids (citric, etc.), alcohol and formaldehyde, are oxidized, and thus disintoxicated. Methenamine is activated by the liberation of formaldehyde in acid urines. The *liver* is especially active in disintoxication, partly by destroying, but particularly by storing poisons, so that the same dose may be less effective when given by the mesenteric than by the jugular vein. This has been demonstrated for curare, strychnine, morphine, cocaine, veratrine, quinine, atropine and the metals. Perfusion of alkaloids, glucosides, toxins, barium, etc., through excised liver decreases their toxicity (Woronzow, 1912). Experiments with Eck's fistula gave rather negative results (Rothberger and Winterberg, 1905). Perfusion through excised *muscle* produced disintoxication, but weaker than the liver, with chloral, atropine, physostigmine, curare and alcohol, not with muscarine and ricin (Woronzow, 1912). The *serum* of atropine-resistant animals destroys atropine.

Disintoxication by Adsorption.—Pilocarpine is detoxicated by digestion with serum, but may be recovered from this in fully active form by extraction with acid alcohol, so that it was not destroyed. The nature of the adsorbing substance is not known. It is abundant in rabbit serum, less in that of cats or oxen, and is absent from dog's blood (v. Leeuwen, 1918, Beutner, 1925).

Disintoxication by Combination.—Phenols and other aromatic compounds are rendered less toxic by conjugation with sulfates; aldehydes, camphor, chloral and ethereal oils by glycuronic acid; many metals by combining with proteins; toxins by antitoxins; acids by alkalis; cyanides by sulfur; benzoic acid by glycocoll, etc. The extent of the disintoxication depends on the activity of the metabolic processes which are concerned, or on the amount of neutralizing substance present in the body.

THE EXCRETION OF DRUGS

This occurs mainly through the urine and feces, and with volatile drugs through the lungs. The sweat and other secretions play a minor part. The relative importance of the different channels varies for each drug, but the urine generally contains considerably more than do the feces. The rapidity is proportional to the circulation and to the functional activity of the excretory organs, and may be increased by the factors which stimulate these.

The urinary excretion varies in general as the plasma concentration (although it is not identical with it). Its rate therefore depends on the speed of absorption. With oral administration, soluble substances generally appear in the urine in five to fifteen minutes, reach their maximal concentration in one-half to one and one-half hours, maintain this to the second or third hour, and then decline gradually. Some 80 per cent of the amount administered is generally excreted in the first twenty-four hours. Traces may be demonstrated for weeks, by remobilization from tissue depots. If absorption is slow, the plateau may be maintained for days. If repeated doses are administered faster than they are excreted, the tissue and urine concentration rise, producing cumulation. Cumulative effects may also result from the summation of injuries or of repair.

Fecal excretion appears to lag behind the urinary excretion, partly because nearly a day elapses before the feces reach the rectum. The fecal excretion is compounded of biliary excretion, which differs for various substances; excretion in the saliva, gastric juice (generally small) and duodenal and pancreatic juice; and cellular excretion by the leukocytes and desquamated intestinal epithelium. *Intestinal excretion* occurs chiefly in the colon.

Excretson by the colon has been confirmed for calcium and phosphate by radio-isotopes (H. W. Florey, Wright and Jennings, 1941). There is also good evidence for the colonic excretion of iron, but no indisputable evidence for mercury, bismuth, neoarsphenamine, mercurochrome or metaphen (I. Leitch, 1936).

Excretion by the saliva is rather limited. It generally begins within twenty minutes and may last over nine hours (Howe, 1912). After intravenous injection, iodide and lithium appear promptly in the saliva; dextrose and ferrocyanide very slowly or not at all (Langley and Fletcher).

The pancreatic juice helps to eliminate some dyes, including acid and basic fuchsin, methylene blue and fluorescein. Crandall *et al.*, 1929, report that it does not excrete thiocyanate, iodide or pyridium.

Sweat excretes a considerable number of drugs, especially chloride, iodide and bromide. The quantities are too small to make them significant for elimination.

Elimination by the lungs through the alveoli is rapid for gases and volatile substances. *Dusts* are actively eliminated from the passages, including the terminal bronchi. This involves ciliary motion, which may propel small particles at 0.25 to 1 cm. per minute in the bronchi, and up to 3 cm. in the trachea (Barclay and Franklin, 1937; Florey, Carlton and Wells, 1932).

Cerebrospinal fluid is secreted or filtered by the choroid plexuses of the brain ventricles. Inorganic substances are excreted into this only in a slight degree; iodides and bromides are generally present. Many organic substances pass into it much more freely. Alcohol, chloroform, acetone and methenamine occur constantly in about the concentration of serum (Hald, 1911).

The passage into the cerebrospinal fluid varies with the *species*. Picric acid penetrates in dogs, cats and guinea pigs, but not in rabbits (L. Stern and Gautier, 1918).

Passage to Fetus.—Soluble substances pass freely across the placental circulation, so that their concentration in the fetal and maternal blood, and indeed in the organs, is practically identical. The more important drugs which have been demonstrated are: ferrocyanide (Mayer, 1871); chloroform, ether, CO, ethyl bromide, atropine, morphine, scopolamine, chloral, salicyl, quinine, benzoic acid, phlorhizin, alcohol, nitrate, urea, methylene blue, As, Hg, KI, KBr (Kehrer, 1907), also bismuth. The placenta acts as an ultrafilter, so that colloidal dyes, and presumably proteins, do not pass into the fetal circulation (Schimidzu, 1923).

DOSAGE (POSOLOGY)

Drugs are administered to produce a desired effect, and the dose must be sufficient for this purpose, and neither too small nor too large. Since the effect is influenced by numerous conditions, it is impossible to state exact doses for any drug; experience is the best guide. The doses vary, however, under ordinary conditions only within rather narrow limits, so that it is feasible to state the *customary* or *average dose*, as is done in the U.S.P. and ia this book; *i. e.*, "the doses which may be expected ordinarily to produce the therapeutic effects for which the preparation is most commonly employed." Unless otherwise stated, these doses apply to adults of average size, and to oral administration. They are not intended to be binding on physicians, but they are convenient approximations for memorizing. The metric and apothecaries' doses in the U.S.P. are not mathematical equivalents, but represent the quantities that would be prescribed under identical conditions by physicians trained respectively in the metric or in the apothecaries' system of weights and measures" (U.S.P.). In this volume the emphasis is on the metric doses, and those of the other system are often omitted if they are not commonly prescribed.

The "*maximum dose*" signifies the largest dose which can be safely used in ordinary cases; the "*minimum dose*" is the smallest dose which produces therapeutic effects; n "*toxic dose*" is one which produces dangerous effects; the "*just fatal dose*" is that which is just sufficient to cause death; the "*physiologic dose*" (a rather indefinite term) is used in physiologic experiments on animals.

Most foreign pharmacopoeias (but not the U.S.P. or B.P.) give tables of "Maximum Doses," not with the purpose of restricting the physician, but as a guide to the pharmacist. He is not permitted to dispense doses larger than these unless the physician indicates specifically that the larger doses are intentional. With some drugs, the fatal and active dose are far apart (atropine); with others, they are close together (strychnine). The distance may vary for different actions of the same drug.

Variations According to Administration.—Different methods of administration, by altering the rapidity of absorption, produce quantitative differences in the effects and therefore in the dosage. Since these vary with each drug, they must be determined by observation. General ratios of oral, rectal and hypodermic doses, supposed to apply more or less to all drugs, are dangerous (Hatcher and Eggleston, 1914). The rectal dose may be larger or smaller than the oral. For parenteral administration, the dosage decreases in the sequence of hypodermic, intramuscular and intravenous. The same dose acts more potently the more rapidly it is introduced, mainly because there is less excretion and destruction before the full dose has entered; also because it reaches the heart and other centers before being distributed through the body.

This must be taken into account in fixing the minimal fatal dose. Extremely rapid intravenous injection may simulate a higher fatal dose if death occurs during the injection, because in this case really more poison may have been administered than was necessary for death (I. Simon, 1905).

Daily Dose.—The single doses are usually calculated on the assumption that sufficient time is allowed to elapse between the doses for the greater part of the drug to be excreted. This constitutes a *periodic medication.* The time varies with the drug, but in most cases the drug is administered three or four times a day; so that the *daily dose* is about three or four times the single dose. If *continuous action* is desired, correspondingly smaller doses are given at shorter intervals.

Single and Divided Doses.—With some drugs a given amount is most potent when administered as a single dose (cyanide, emetine, strychnine), while others (strophanthin, chloral, salicylate, heroin, antipyrine) appear more potent when fractional doses are repeated at close intervals (Uchida, 1926).

Effect of Weight.—Other things being equal, the effect of a given dose is inversely proportional to the weight of the individual (exclusive of the adipose tissue). This may be used for calculating the doses for children. It is generally not necessary to make allowance for the weight of adults (twenty to sixty years).

Body surface is regarded by some as a more accurate although less convenient index of the dose (Moore, 1909; Dreyer and Walker, 1914); but the subject is in dispute (Kisskalt, 1915). It probably applies only to heat production; for other actions are proportional to the concentration of the drug, and this varies with the mass, not with the surface. It is not strictly proportional to the weight, however, since the drugs would not be uniformly distributed through the tissues. The early distribution of soluble drugs is in the *extracellular fluid*, averaging 20 to 30 per cent of the body weight, or about 15 Kg. in an adult. The *maximum percentage concentration of the drug in contact with the cells* would therefore be the dose in grams divided by 150.

Calculation of Doses for Children.—In most cases the adult dose is reduced in simple proportion to the weight of the child—either by direct calculation or by the use of empiric rules based on averages, as described below. The dosage so obtained is generally sufficiently exact. It is inadmissible only with extremely young children, and with drugs the action of which is influenced specifically by age.

Clark's Rule.—Multiply the adult dose by the weight of the child (in pounds) and divide by 150 (the weight of the average adult). This rule gives the best approximation.

Cowling's Rule.—Multiply the adult dose by the age of the child at the next birthday, and divide by the adult age, taken as twenty-four. *For instance,* the dose for a child of three years would be $\frac{4}{24} = \frac{1}{6}$ of the adult dose. This rule gives data agreeing sufficiently well with the average weight curve, more accurately than Young's Rule. The results are rather too low, below four years and above fifteen years, but the error is on the safe side.

Young's Rule: Multiply the adult dose by the age of the child (in years) and divide by the age plus 12. *For instance,* the dose for a child of three years would be $\frac{3}{15} = \frac{1}{5}$. As compared with Cowling's Rule, it gives somewhat higher doses below twelve years, and somewhat lower above this age. *Fried's Rule:* Divide the age in months by 150 and multiply it by the adult dose; *f. i.,* for a baby of five months, the dose would be $\frac{5}{150} = \frac{1}{30}$.

The dose for aged people is generally taken as somewhat less than that for adults. Above sixty years, the adult dose is reduced to four-fifths or two-thirds, and in extreme senility to one-half.

Specific Influence of Age on Drug Action.—These (*i. e.,* apart from the difference due to weight) are known definitely only for a few drugs. *Children* are comparatively tolerant to cathartics, strychnine, iodides, iron, belladonna, calomel, digitalis and sparteine (A. Jacobi, 1907). *Old age* is generally less resistant to drugs; purgatives and emetics are especially debilitating. The existence of atheroma makes it dangerous to use drugs which raise the blood pressure.

Clinical age relations are not substantiated by adequate data. *In animals,* K. K. Chen and Robbins, 1944, found the following: *Histamine* by vein is less toxic to guinea pigs younger than ten days; but this does not hold for hypodermic injection. *Morphine* intravenously is more toxic to fourteen day old than to older rats. *Picrotoxin* is more convulsive to two year old mice than to the younger animals. *Alcohol* hypodermically is more toxic to the older rats. Each substance has its own characteristics.

Influence of Sex.—Women usually require somewhat smaller doses than men (one-half to four-fifths). The greater susceptibility is in large part due to the lesser weight, but in part also to the anatomic and functional peculiarities. The influences of sex are of course most pronounced with drugs which act on the generative organs. **Pregnancy** contraindicates the use of irritant cathartics (because of the danger of inducing abortion) and of irritant diuretics (on account of the tendency to nephritis).

"Minimal lethal dose" (M.L.D.) determinations on animals are important for bioassays and the evaluation of margins of safety, and the efficiency of antagonists. Individual animals may differ considerably from the average, due to differences of absorption and other factors. This results in sigmoid "frequency distribution curves" (Trevan, 1927; Durham, Gaddum and Marchal, 1929; Munch and Garbugh, 1935; C. I. Bliss, 1935), which vary considerably even for related substances (Dawson and Little, 1937). The dosage by which 50 per cent of the animals die (designated "LD_{50}" or "FD_{50}") gives the most consistent data and is now generally adopted.

Tiffeneau, 1931, proposed 75 per cent survival as "tolerated dose" and 25 per cent survival as "fatal dose." It is also necessary to set a time limit for fatality, varying for different drugs. The use of logarithmic paper for simplifying probability calculations is described by Prigge and Schäfer, 1939.

INFLUENCE OF CONDITIONS ON DRUG ACTIONS

Pharmacologic reactions vary with the concentration of the drug and with the excitability of the tissues. The latter is influenced by physiologic and pathologic conditions; and among the latter, by the simultaneous action of other drugs.

Quantitative Relation of Concentration and Action.—The pharmacologic response tends to increase with the concentration of the drug; but not generally in simple proportion. There is usually a "minimal threshold," all concentrations below this being apparently ineffective. At the other extreme, once the "maximal response" has been reached, further increase of concentration can produce no further effect. Between these points, every increase of concentration increases the action, generally as a logarithmic function; *i. e.,* the increment being the greater the lower the original concentration, in accordance with the Weber-Fechner law of stimulation.

For instance, when the concentration of ouabain was doubled from 0.00125 to 0.0025, the action was increased 4.6 times; when the concentration was doubled from 0.005 to 0.01, the action increased only 1.28 times (Sollmann, Mendenhall and Stingel, 1915; the paper also discusses the reasons for the phenomenon.) Data on the concentration relations of other pharmacologic phenomena are given by Shakell, 1924.

In some cases it appears as if the drug acts only while passing through the cell membrane, a phenomenon that has been termed "*exodic gradient*" (Straub, 1907; Trendelenburg, 1912; Kuyer and Wijsenbeek, 1913; H. Gremels). This may be due to phase-boundary electric potentials, such as are produced by acetylcholine solutions in contact with cholesterol (Beutner and Barnes, 1945). Sometimes the phenomenon is an artifact. Sigmoid curves are often due to errors of recording apparatus.

Qualitative (Directional) Changes with Concentration.—Pharmacologic stimulation may pass gradually into depression when high concentrations are employed—somewhat analogous to colloidal solutions which flocculate and precipitate when their reaction is neutralized to the iso-electric point, but which dissolve when this point is passed by further addition of the neutralizing agent. Such *diphasic actions*, constituting the "Arndt-Schulz Rule," are fairly common, although far from universal. They have been invoked by Hahnemann and other homeopathic writers in support of the "doctrine of similes," that infinitesimally small doses of drugs should combat symptoms analogous to those produced by larger doses; an assumption which led to some fantastic corollaries.

Multiple Independent Actions.—The relation to the concentration becomes complicated if the drug produces several effects with different optima. This gives rise to *polyphasic variations*, which are often difficult to disentangle. For instance, relatively low concentrations of chloroform depress muscle by liposolvent surface action; high concentrations precipitate the protein within the muscle cells, producing rigor.

The Combined Action of Drugs.—The effects of drugs are influenced by the unusual conditions induced by the simultaneous administration or presence of other drugs. A quantitative change may occur either in the sense of increasing the efficiency (*synergism*) or of diminishing it (*antagonism*). There may also be qualitative changes. New actions may be developed by the reaction of the drugs on each other, with the production of new compounds: acids render the basic salts of bismuth soluble and toxic; oxidizing substances may liberate iodine from iodides; the iodides also decompose calomel and render it irritant. Antagonism of action is employed in the treatment of poisoning, or sometimes to remove undesired side effects. When it interferes with desired effects, it constitutes "*therapeutic incompatibility.*"

Combination Therapy.—Synergism is utilized to secure the summation of the desirable effects of several drugs, while the side actions are not increased in proportion, or may even be neutralized. The potency may be increased, especially when the drugs attack a given cell or function simultaneously by several different mechanisms. Combinations of drugs were formerly popular on the empiric principle of the shot-gun mixture—that of many ingredients, some at least might fit the disease. It is better to employ the fewest possible drugs, until it has actually been shown that combinations give superior results in the particular condition. In giving several drugs of similar actions, the dosage of each must be correspondingly reduced.

Variations of Combined Action.—When several drugs are administered together, each may act independently, as if it were present alone. The result would then be a *simple algebraic summation* of the effects, either synergistic or antagonistic. In many cases, however, the combined action is greater or smaller than would be calculated (*potentiated* and *deficient summation*). If the action of two agents is really identical, their mixture would be equivalent to increasing the concentration of either, and would therefore follow the Weber-Fechner law of diminishing returns and appear deficient. This *complemental synergism* is a means of confirming identity of action. *Potentiation or supplemental synergism* occurs only if the two agents have different points of attack in the cell. W. F. Buergi (1910, 1926) formulated this as "*Buergi's law,*" but Fuehner, 1912, Issekutz, 1913, Zorn, 1913, and others have pointed out numerous important exceptions. It is certainly not universally applicable.

The simple lipolytic narcotics (alcohol, ether, chloroform, etc.) show practically only simple summation; but the addition of the alkaloidal narcotics (morphine and scopolamine) gives considerable potentiation (Knell, 1907; Fuehner, 1911; Kochmann and pupils, 1913). Bromides give simple summation with lipolytic and alkaloidal narcotics (Klammer, 1913). The different opium alkaloids potentiate each other in interesting ways (Straub, 1913; Macht). The organic local anesthetics do not usually potentiate (Schmid, 1913). Fuehner, 1912, worked out the summation of hemolytic agents.

Modified Synergisms.—The relations may vary at different dose levels: Stimulants are antagonistic to depressants only in small doses. Large doses often become synergistic, the depression being greater than if the depressant were used alone. Instances of this are atropine and pilocarpine on embryonal growth (Sollmann, 1904); caffeine and alcohol toxicity (Pilcher, 1912); atropine and physostigmine toxicity (Fraser). The effects of autonomic drugs are generally enhanced by previous exposure of the excised organs to *colloids* or colloidal precipitants (Thienes, 1926).

Cumulative action exists when continuation of a given dose of a drug produces greater effects than the first doses. It may be due to an actual accumulation of the drug, absorption being greater than the capacity for excretion; or it may result from summation of effects, when the changes brought about by the first doses persist; the drug may use up some substance required for its disintoxication (phenol); or there may be general decrease of resistance, sometimes by actual injury.

Inconstant absorption is a frequent cause of apparent cumulative action. Successive doses of the drug may lie unabsorbed in the alimentary canal, to be finally taken into the system *in toto* when the conditions are favorable to absorption. This explains the greatest individual variability to toxic doses for those drugs which are absorbed with the greatest difficulty.

Irregularities of excretion (nephritis, etc.) are favorable to the development of cumulative effects.

"*Education*,"—Effects are sometimes more easily reproduced after they have once been induced. This is seen particularly in the central nervous system. The susceptibility to strychnine, for instance, is said to increase with its administration.

Tolerance may be due to nonabsorption, to rapid elimination, to neutralization or destruction of the poison, or to anatomic peculiarities. Many cases appear to be functional (the "histogenetic" immunity of Behring). The tolerance is rarely absolute, so that it is incorrect to speak of "immunity." Tolerance may be congenital or may be developed by the repeated administration of the poison. This *habituation* may be by functional adaptation (alcohol, caffeine, nicotine); or it may be due to diminished absorption (arsenic) or increased elimination (atropine in cats); or to increased destruction of the poison (atropine); or to the production of antibodies (toxins). The tolerance is usually limited, not absolute. Tolerance to habit-producing drugs is largely psychic: The nervous centers learn to modify their reactions so as to adapt them to the drug environment. When this environment is abruptly altered by the withdrawal of the drug, there is generally extreme discomfort, resulting in craving and great nervousness, constituting "*abstinence symptoms.*" Functional habituation, acquired for a particular drug, may hold also for other drugs having a similar action. A habitual drunkard, *e. g.*, is resistant to the general anesthetics; morphinists are said to be more tolerant to cocaine (Chouppe, 1889). Tolerance is not acquired to convulsive poisons (W. Biehler 1935).

Antitoxin formation is a conspicuous instance of acquired tolerance. It is chiefly confined to proteins, and does not occur with alkaloids or any of the simpler poisons.

Acquired immunity in protozoa has a practical as well as theoretic bearing on chemotherapy, and has been investigated by Ehrlich, 1909, and Neuhaus, 1910. These organisms acquire immunity for several groups of poisons—metals and dyes—the tolerance induced by one drug applying to other chemically related drugs, but not to the other groups. The immunity, when once induced, is transmitted unlimited from generation to generation. The adaptation may consist merely in the selective propagation of the naturally more resistant individuals (mutants), *i. e.*, in the "survival of the fittest." With alkaloids, Prowazek, 1910, found that different individuals, even in the progeny of a single parent, show varying resistance to the same alkaloid. Single cell cultures of various *bacteria* adapt themselves to concentrations of NaCl, $HgCl_2$ and $CuSO_4$ considerably higher than are tolerated by nonadapted strains. This specific resistance is retained by the descendants (Severens and Tanner, 1945).

Idiosyncrasy.—This term (from ἴδιος, one's own, and σύνκρασις, a blending) is applied to exceptional reactions to the effects of drugs. They may consist in quantitative hypersusceptibility to the ordinary actions of the drug. Such hypersusceptibility is especially conspicuous if it emphasizes a side action that is ordinarily negligible. Neurotic individuals are subject to psychic exaggeration or modification of drug effects through fright, excitement or suggestion. *Allergic hypersusceptibility* is a special type of idiosyncrasy in which the patient reacts to special substances, foods or drugs by irritative edema and spasm of smooth muscle, urticaria, bronchial asthma and collapse. It is generally hereditary, but not congenital; *i. e.*, it may not manifest itself till later in life. It usually resides in the tissues, so that it cannot be transferred by the blood serum. Allergic hypersusceptibility may be induced in excised tissues by treatment with colloidal precipitants (Thienes, 1926).

Sensitization or induced drug allergy, more or less analogous to protein anaphylaxis, may develop some five to twenty days after the administration of certain simple chemical compounds, such as iodide and bromide ions. Regular daily administration is less likely to produce sensitization than intermission of seven to ten days between doses. Landsteiner and van der Scheer, 1933, explain sensitization by the assumption that non-protein chemicals of many types combine with body protein to produce substances with antigenic properties.

When this has occurred, the chemical itself reacts directly with the antibody (also *in vitro*) to produce an immunological response which constitutes the hypersusceptibility. Willstätter and Rhodewald, 1934, postulate "*symplex compounds*" formed by the combination of a prosthetic group with compounds of high molecular weight. The potency of the prosthetic group depends on some special configuration rather than on a special element. The activity may be lost by the destruction (or denaturation) of either the prosthetic group or the colloidal carrier.

Quantitative racial differences exist in the skin and iris, and are probably related to the structure and pigment. Dark races are less susceptible to cutaneous irritation, especially by radiation and by chemicals ("mustard gas," petroleum products). Their iris is less responsive to mydriatics.

Impurities of Drugs.—Abnormal reactions may sometimes be due to impurities, but this is rather exceptional. Minimal amounts of foreign substances are not very objectionable unless they are poisonous. The pharmacopoeias permit the presence of small amounts of such innocuous impurities which it would be difficult and costly to remove.

Individual Idiosyncrasy in Animals.—In animals, as well as in man, peculiarities exist in different individuals of the same species. *Qualitative differences* are seen particularly in the action of narcotics on higher mammals. Instances of *quantitative differences* are numerous: In any large series of experiments there is a fair degree of uniformity in the proportion of animals which die with a given dose. The variation for three deaths in five animals ranges from 0.5 per cent (strychnine) to 25 per cent (ergot), but is usually comprised within 5 to 10 per cent. The susceptibility of any one animal is subject to greater possible variations; *e. g.*, with a given preparation of digitalis, 0.6 mg. per gram always kills three guinea pigs out of five; but in a large series, a number of animals die with 0.4 mg., while others die only when 0.9 mg. is reached.

Racial Idiosyncrasy in Animals.—Different kinds of animals may differ in their reaction. This can usually be explained by *differences in the physiologic functions.* Cerebral actions are usually the more pronounced, the more highly the central nervous system is developed; spinal actions predominate in the lower vertebrates; rodents are incapable of vomiting. Atropine quickens the heart action of the dog, but not that of the rabbit, because it acts by paralyzing the vagus, which is not tonically active in the rabbit. The dogfish, which is more or less resistant to nephrotoxic poisons, normally excretes urea and probably other metabolic products mainly by the intestines and bile (Denis, 1913). Natural resistance is often due to the destruction of the poison, *f. i.*, that of atropine by the serum of rabbits, etc. Differences of absorption and excretion also come into play.

Differences which cannot yet be explained on a physiologic basis may be referred to ignorance of the physiologic differences which are involved. The *hedgehog* has a high unexplained resistance to many poisons: morphine, atropine, nicotine, cyanide, cantharides, arsenite, diphtheria and tetanus toxins; not for strychnine (Strubell, 1909; Willberg, 1913). *Birds* react to most poisons qualitatively like mammals, although there are quantitative differences in both directions. Cocaine, however, lowers their temperature (Forchheimer, 1931). Even the same *organs* in different classes of animals may show unexplained differences. Thus, Gunn, 1909, claims that apocodeine, quinine, and yohimbine, which cause vasodilatation in mammals, constrict the blood vessels in frogs—both peripherally.

Influence of Pathologic States.—The effects of drugs in disease may differ from those on healthy animals. The pathologic conditions may diminish absorption (diarrhea) or increase it (corrosion); they may hasten the destruction of the poison (alcohol produces less intoxication in fever); or they may alter the effects entirely. Some of these modifications are explained by the functional or anatomic changes of disease; others are obscure. In judging the effects of drugs on disease, it must not be overlooked that abnormal conditions naturally tend to return toward the more stable equilibrium of the normal, so that comparisons must be controlled by the untreated disease, and not merely by the effects on normal individuals (F. T. Jung, 1938).

Antipyretics reduce the temperature in hyperpyrexia, but do not affect it when it is normal; digitalis is an efficient diuretic in cardiac disease, but not in health; the antiseptics and antitoxins are active only in infections, etc. Numerous other instances may be found in the papers of Salant, 1911, and Wallace, 1912.

Pathologic conditions which modify *absorption and excretion* are of particular practical importance; suppression of urine, as by nephritis, may lead to toxic symptoms from drugs or doses which are ordinarily harmless. The general reduction of vitality, the "*lowered resisting power*," which is common in many diseases is similarly important.

Lusini and Sebastiani, 1906, found the absorptions of poisons hastened immediately after *hemorrhage* but not later. The toxic symptoms were not modified. The resistance was found lowered to a varying degree for different poisons: most for strychnine, less for veratrine, and not at all for physostigmine. Wiggers, 1910, found that severe hemorrhage paralyzes the vagus center and thus alters the response of the heart rate to epinephrine, digitalis and nitrite.

Inflamed vessels react abnormally. Eskin, 1914, found constrictor drugs generally less and dilator drugs more effective. Epinephrine often produced dilatation, while caffeine, which normally dilates, constricted the inflamed vessels of rabbit's ear.

The distribution of the drugs in the body may differ in disease and health. *Inflammation* increases capillary permeability; but the coagulation of the inflammatory exudate soon walls off the area (Menkin, 1931–1933). Iodide and many dyes tend to accumulate in the necrotic areas of tuberculosis and tumors (Cecil and Weil, 1917).

Seasonal variations exist in the susceptibility of animals to a number of poisons. With cold-blooded animals, this would be referred partly to differences of temperature; but considerable variations exist also in mammals. Guinea pigs are more resistant to ouabain, and less resistant to acetonitrile and diphtheria toxin during November to January than in the spring and summer months (Haskell, 1912). Seasonal changes in internal secretions, connected with the sexual activity, probably play a prominent part. Seasonal diet is also an important factor.

Diet has a marked effect on the resistance of animals to many poisons (Hunt, 1910; Opie and Alford, 1914). The people of the undernourished war countries were said to show greater susceptibility to the toxic manifestations of mercury and arsphenamine, to the narcotic action of morphine and to cutaneous reactions for various drugs (Zernick, 1919; Rumpel, 1919). The calcium content is important in influencing cutaneous irritation (Luithlen, 1911, 1912). Barium is better absorbed from a Ca-poor diet (Alsberg and Black, 1912), as is also lead. The acid-base content of the food is an important factor in relation to renal irritations (Salant and Bengis, 1917; MacNider).

Ion Ratios.—The responses of excised or perfused tissues, especially to the autonomic poisons, are modified by the hydrogen ion concentration and the ratio of calcium, potassium and magnesium ions (Salant, 1924). They are of minor importance in the living body, which does not readily change its normal ion ratios.

Temperature influences pharmacologic effects, especially in cold-blooded animals and in excised organs, since heat speeds up chemical and especially enzyme reactions. In warm-blooded animals it affects the responses of the temperature centers, so that dinitrophenol tends to raise the temperature in a warm room, and to lower it in the cold. Warm temperature also increases the action of drugs on and through the skin, by maceration of the epidermis with sweat. This is conspicuous in industrial poisoning.

The influence of body temperature on drug action is reviewed by F. A. Fuhrman, 1946. In cold-blooded animals, colchicine, picrotoxin, strychnine, tetanus toxin, digitalis, veratrine, nicotine, chloral, atoxyl, and alcohol are rendered more active, morphine and curare less active, by raising the temperature; physostigmine, epinephrine and many others are not affected (Fuehner and Breipohl, 1933). The *temperature quotient* of strychnine was investigated by Schlomovitz and Chase, 1916. The temperature coefficient of most pharmacologic actions is $Q_{10} = 2$ to 4. As the reactions of cells are of the nature of chain processes, the limit is set by the slowest link, and the quotient gives no information as to the nature of the process as a whole (A. J. Clark, 1937).

Colchicine is four hundred times more potent for frogs at 30° C. than at 19° C. (Fuehner, 1910). Mice are also four hundred times more sensitive to colchicine than are frogs at room temperature so that the heated frogs react as warm-blooded animals (Fuehner and Wagner, 1932). With *muscles*, the activity of drugs increases in a mathematical ratio with the temperature within certain limits (Veley and Waller, 1910). The temperature relations of digitaloids are discussed by Sollmann, Mendenhall and Stingel, 1915. In mammals, cooling generally increases toxicity by adding its direct depressant action. *The effect of temperature on spinal reflexes* was studied by van Leeuwen and van der Made, 1916, in mammals and frogs.

THE MANIFESTATIONS OF PHARMACOLOGIC ACTIONS

Pharmacologic agents rarely if ever create new functions in a cell or tissue; they only modify existing functions or make evident functions which have previously been latent. The functions of a cell may be increased or diminished, resulting in *stimulation* or *depression*. Since there are also structures the stimulation of which would lead to an inhibition of other structures, an actual increase of function is sometimes distinguished as *augmentation*. A violent stimulation passes usually into injury; such injurious stimulation is called *irritation*. Moderate but prolonged stimulation may pass into depression, either by the disappearance of food substances (*exhaustion*) or by actual injury to the structure (*fatigue*). If the depression is so great that the given function has disappeared, the condition is called *paralysis:* if all the functions are abolished, there is *death*. The greater number of pharmacologic agents produce at first a stimulation, which is followed in large doses by depression. In this respect the differences between the different poisons are again mainly quantitative. The so-called "stimulants" produce strong and prolonged stimulation, the depression being noted only with relatively large doses. The "depressants" cause only slight stimulation, which passes readily into depression. With some depressants, no stimulation whatever exists. It is rare that a depression precedes a stimulation; when this occurs, the action is presumably on different structures.

Selective Action.—The actions of drugs are generally much greater on some tissues than on others; *i. e.*, they are selective. The difference may be almost or quite *absolute*, so that the drug acts specifically on one class of cells. This "monotrope" action is important in parasiticides, and was Ehrlich's ideal of "*chemo-therapy*," the treatment of infections by chemic agents. Antibodies also illustrate a strickly monotropic selective action. With many drugs the differences are merely quantitative or *relative*, a number of structures being affected with various degrees of predilection, which may sometimes shift with changing conditions. The actions on the central and peripheral nervous systems generally belong to this relative type. *The mechanisms of selective actions* may consist in differences of penetration; of the chemic affinities of the cell; or of sensitiveness of the functions. The details are known only in a few cases.

Surface and Interior Actions.—A drug may act upon a cell without actually penetrating into it; for instance, by exciting the nerves supplying the cell or, more directly, by withdrawing water from the protoplasm; but as a general rule the poison must be absorbed into the cell or cell membrane before it can produce any action. In order that this absorption may take place, the drug must be soluble in the cell contents, and particularly in the cell envelope. The solubility of a substance in protoplasm is not necessarily the same as in water; it varies for each kind of cell, and consequently the penetrability of different cells for a given substance may vary greatly.

The quantity of a substance that enters a cell may be considerable and come within the compass of ordinary chemical reactions, even if the effects are produced by high dilutions. This holds especially if the substance undergoes selective concentration, sometimes to a thousandfold the concentration of the solution, particularly if the drug acts on the cell surface. The action in that case has no relation to the amount taken into the cell. In other cases the amount may be too small to cover the cell surface even with a monomolecular layer. It may then be assumed to act selectively on some constituent. When a drug acts on enzymes it may start a chain of events that may be far-reaching (A. J. Clark, 1937).

Ouabain is fixed by the heart of frogs and cats in the ratio of $2:10^6$, which has been calculated to cover less than 3 per cent of the heart cells with a monomolecular layer (Clark, 1933). Similar relations exist for acetylcholine and epinephrine.

The action of *inorganic catalysts* may be inhibited by poisons in amounts too small to cover their surface, so that the action must be limited to foci or "patches" on which the poison condenses. Rapid adsorption on the surface, followed by slow diffusion into the interior, is frequent in inorganic systems, for instance the adsorption of oxygen by charcoal, and illustrates what commonly happens with cells.

Intracellular administration by direct micro-injection may be quite ineffective compared with surface application, indicating that in these cases the drug acts on the cell surface. Instances are cyanide and hydrogen sulfide on Amoeba proteus (F. J. Brinley, 1928) and methylene blue on frog ventricle (R. P. Cook, 1926). Phenol, on the other hand, penetrates into the cells and disorganizes their protein structure.

Selective Absorption.—Absorption into cells is generally much better for nonionized compounds, for instance for free alkaloids (Overton, 1897); CO_2 and H_2S (Osterhout, 1925); and arsenious acid (Hoskins, 1932). All cell membranes, however, are somewhat permeable to ions (U. Friedemann, 1942).

While renal cells are very permeable for sulfates, intestinal cells are but slightly permeable. This peculiarity enables cells to preserve their own composition, notwithstanding considerable changes in the fluids in which they are bathed. It also explains why a given substance acts much more strongly upon one cell than upon another. It is illustrated by the distribution of *dyes* in living and dead tissues; or, indeed, in unorganized materials. Lipid solvents generally penetrate better than other agents, because of their affinity for the lipid constituents of the cell membrane. Other agents probably form "solid solutions" with some of the cell constituents; others are attracted by chemic differences—*e. g.*, the basic stains by the acid character of the nuclear chromatin. Adsorption and surface forces probably play an important part.

Selective Absorption into Pathologic Tissues.—The distribution may be modified by reaction, oxygen, the presence of a second substance, etc. Important differences arise also in diseased conditions, *e. g.*, iodides are taken up in higher concentration by degenerating tissues. Tuberculous caseous tissue has this property of condensing iodides and dyes, especially those of the safranine and acridine groups (A. Lewis, 1917). Other inflamed tissues and inflammatory products also tend to take up dyes (Cecil and Weil, 1917). Trypan red appears in the aqueous humor much more readily when the eye is inflamed or when physostigmine is applied (P. A. Lewis, 1916). The feeding of *madder dye* stains bone and pathological calcareous tissue *in vivo*, probably by forming calcium alizarate (Macklin, 1917).

Functional differences may simulate selective action, *the more delicate functions being damaged more readily.* Hence a poison which acts indifferently on all tissues produces the most conspicuous effect on the central nervous system.

CLASSIFICATION OF DRUGS ACCORDING TO SELECTIVE ACTION

Poisons which produce effects at the place where they are applied are termed "*locally-acting*" drugs. They may produce similar chemic changes in dead tissues. These usually cause inflammation when applied to living structures, and are then called *irritants* (including simple irritants, corrosives and astringents). Others lessen inflammation mechanically (emollients and demulcents). Others act chemically on all living structures, without changing dead tissues; these are termed "*protoplasmic poisons*." Poisons which act selectively on a few structures are called "*muscle-nerve poisons*." They may affect end-organs (sensory endings, gland cells, or striped, smooth or cardiac muscle); or the nerve endings; or ganglia; or any part of the central nervous system. *Nerve trunks* are so protected by their sheaths and by their limited blood supply that they are only affected when the poison is applied to them directly.

Systems of classifying drugs with systemic actions are unsatisfactory, because most drugs produce several effects which, by their interaction, complicate the subject so that no simple system will apply. With some drugs, one pharmacologic, chemic or physical feature predominates so greatly that they can be separated as fairly distinct groups.

The selective action of drugs is rarely absolute. When some one action is so predominant that it may be considered as the characteristic of the drug, there are generally other actions, especially when conditions are altered: even strychnine, a highly selective convulsant poison, acts as a general protoplasmic poison when it is directly applied in sufficient concentration. This accounts for the great variability which is often seen in the action of the same drug under different conditions. Atropine stimulates the vagus center, but paralyzes the endings; it may therefore cause either a quickening or a slowing of the pulse. Another frequent cause of variable actions lies in indirect actions: A drug which causes convulsions thereby tends to stimulate the vasomotor center, although its direct action of this center may be depressant. These variable actions and interactions make the effects of many poisons appear complicated, although they may prove quite simple on analysis. This analysis is important for a proper understanding of the action, but it is still more important to remember the complex effects which result, for it is with these that the practicing physician has to deal.

The pharmacologic action in this sense is often not the therapeutic action. An important pharmacologic action of morphine is stimulation of the spinal cord; but it is not used therapeutically for this purpose, since this action is overshadowed by its other effects. For this reason it would not be advisable to classify drugs strictly according to their pharmacologic actions. On the other hand, a *therapeutic classification* is not favorable to a study of the underlying actions of the drugs, and tends to empiricism Buchheim (the founder of modern pharmacology, by the establishment of the first pharmacologic laboratory at Dorpat in 1856) compromised by grouping drugs according to their principal pharmacologic characters, taking account of all the important actions, as well as of the chemic properties, and in many cases also of the therapeutic uses of the drugs. This is the general objective in this volume.

Definitions of Pharmacologic Terms.—Some rather loosely used pharmacologic terms may be defined in this place, in the sense in which they are generally employed in this volume:

Local actions: produced at the place where the drug is applied. *Remote actions:* occurring in distant parts of the body; they may be either systemic or reflex. *Systemic effects* (sometimes called general action): produced after the absorption of the drug into the circulation. *Direct effects* (sometimes called primary): produced by the direct action of the drug on the tissue concerned. *Indirect effects* (sometimes called secondary), are not produced by the action of the drug on the tissue concerned, but by the intervention of some other structures on which the drug acts (*e. g.*, asphyxial convulsions are an indirect effect of asphyxiant poisons). *Reflex effects* are indirect actions arising from local irritation. *Immediate effects* (also sometimes called primary) are the effects resulting at once. *Late effects* are those occurring later; if they are preceded by other (immediate) actions, they may be called *secondary actions. Side actions* are actions which are not desired in the therapeutic use of the drug, producing untoward effects.

Localization of action involves the methods of experimental physiology:

The Study of Isolated Structures.—To eliminate the complications which arise from simultaneous actions on several structures or from indirect actions, the tissues to be studied are generally isolated. The most certain method is the actual anatomic isolation of the structure. Drugs of known antagonistic actions may also be utilized, but they are likely to lead to erroneous conclusions. The method that gives reliable results with *the least difficulty of technic* is preferred. Complete isolation is in many cases superfluous. If the question is, whether an observed *stimulation* is of a central or of a peripheral structure, it suffices to divide the nerve: on an efferent chain, this abolishes the effects of a central stimulation, while those of a peripheral stimulation persist. With an afferent chain the conditions would be reversed.

A few examples may illustrate this general method:

1. *Strychnine* produces a tetanus. This implies motor stimulation somewhere. The sciatic nerve is cut; it is found that the convulsions disappear in the leg but persist in the rest of the body. The action must therefore be central. The cerebrum and medulla are successively excised; the convulsions persist, and must, by exclusion, be located in the cord. This is confirmed by destroying the cord, which causes the complete disappearance of the tetanus.

2. *Curare* produces complete muscular paralysis. Stimulation of the sciatic elicits no response. The paralysis must therefore be peripheral. Direct stimulation of the muscle is effective. This excludes all the possible structures except the nerve trunk and endings. The nerve of another preparation is laid into the curare solution, and after a time is stimulated; a contraction results, so that the nerve trunk is not paralyzed. The action must therefore be on the endings.

If a peripheral structure is stimulated or paralyzed, it is impossible to decide by this method whether there is not also a central action, for the peripheral effects would obscure the central. Stimulation of the cord, for instance, could cause no effect if the drug had paralyzed the motor endings. In these instances, it is necessary to confine the action of the drugs to the centers.

The Study of the Effects of Drugs on Intact Normal Animals.—A complete conception of the actions of a drug can be obtained only by integrating the study of its effects on isolated structures with careful observation and analysis of the symptoms which it produces in intact mammals. The effects on metabolism, and the histologic lesions, etc., can only be studied in this manner. These experiments are generally undertaken before the more difficult investigations on isolated structures, for they furnish valuable hints of the direction which the latter should take. When circumstances permit, it is advisable to proceed from the lower to the higher classes of animals, and finally to man. Opportunities of observing the *effects of drugs on man* occur in cases of poisoning, but intentional experiments with drugs on man are to be undertaken only with the greatest caution, with doses which do not exceed the therapeutic maxima; and, as a rule, only after the effects have been thoroughly studied on animals. The lower aquatic animals may be used for a preliminary survey if their differences are kept in mind (Daphnia; T. Sollmann and Webb, 1941).

The Effects of Drugs in Disease.—The action of drugs is not always the same in disease as in health. The differences are as a rule quantitative rather than qualitative.

Animal experiments are of limited value in this connection. Observations on patients must be made accurately, psychic factors excluded and the existing pathological condition correctly known. These requirements are not fulfilled in many cases, which accounts in part for the differences which are occasionally noted between clinical and experimental data. Clinical tests of the older drugs have been made so abundantly that further observations might seem superfluous; but accurate observations in the light of advancing knowledge, and employing the improved methods of diagnosis and observation, are always needed. It is highly desirable that every physician should obtain his knowledge of the therapeutic action of drugs at first hand. He should utilize every case under his care for this purpose, and conduct his treatment as if it were a critical experiment, the interests of the patient being, of course, paramount. The conclusions will be greatly simplified if but one drug is used at a time.

Transfer of Results of Animal Experimentation to Man.—The utilitarian aim of pharmacology is to supply medicine with a scientific basis for the practice of therapeutics and for the study of toxicology. This can be attained only by experimentation on lower animals. This brings up the fundamental question: *To what extent can results observed on animals be transferred to man?* The same question applies to all other fields of experimental medical research, and has been abundantly answered by their results. *A similar physiology implies a similar pathology and pharmacology.* In the majority of cases, similar structures are affected in the same way by a given drug, no matter in what animal they are studied. Where differences exist, they can usually be explained by differences of physiologic function. They are now generally recognized so that suitable species can be chosen for experimentation. They can be eliminated further by using the drug on several species: *If a given poison affects all species alike, it may be concluded that its action on man is also the same.* If it produces different effects, which can be explained by differences in physiology, the effects on man will be similar to those produced on the species the physiology of which resembles most closely that of man.

Value and Limitations of Experimental Pharmacology.—Care must be used in applying the results of experimental pharmacology to man. The neglect of this precaution, the drawing of far-reaching conclusions from limited experiments is seen all too frequently. Pharmacology can not be held responsible for misapplication of its data. Its scope is limited primarily to its own results and not to their application, although it may legitimately suggest the latter. It should not be made to replace therapeutics, but should aim to place well-studied tools in the hands of the latter. If this limitation is realized; if the therapeutist will carefully study the results of pharmacology and will utilize and interpret them in the light of bedside experience, then pharmacology will be of great value to medicine. An important service is rendered by pharmacology through the examination of new remedies. The development of synthetic chemistry has resulted in the discovery of a large number of new substances of some therapeutic value. The number is so large that all could not be given a thorough trial on patients. Most of these substances possess some value, but many differ from each other by insignificant details. In this case, pharmacology can select the most promising and, by their thorough study, indicate those which are worthy of trial by the clinician. *The laboratory and clinical appraisal of new drugs* is outlined by W. Van Winkle *et al.*, 1944.

THE CHEMICAL AND PHYSICAL BASIS OF PHARMACOLOGY

Scope of Pharmacology.—The term *Pharmacology* in a general sense covers all scientific knowledge pertaining to drugs, *i. e.*, to substances which may be used in the treatment of disease. *Materia Medica, Pharmacognosy* and *Pharmacographia* have the same meaning when they are used in a general sense. Commonly, however, the term "pharmacology" is used in a more *restricted sense,* as a synonym for *pharmacodynamics.* It concerns itself with the actions of drugs on living structures, or with the reactions occurring between drugs and living structures. It is therefore a branch of physiology on the one hand, of chemistry on the other; and is essentially a division of biology. It has important practical relations with *toxicology* (the science of poisons), and with *therapeutics* (the treatment of disease). A. J. Clark defines "*general pharmacology*" as dealing with the mode of action of drugs.

The Nature of Pharmacologic Action.—The processes of life are conditioned by chemical and physical changes in the constituents of the cells. Foreign chemic substances may enter into these reactions and thus modify them more or less profoundly, with corresponding changes of function. These are termed *drugs* or *poisons,* according to whether they are useful or harmful in a given case. Some of the reactions are comparatively simple, analogous to those produced on isolated proteins. Others involve enzymes; others occur only in living substances. Some compete for substances needed in normal metabolism (review, L. Young, 1939).

Physicochemical Conditions of Life.—The chemic decompositions and syntheses, reductions and oxidations, which are constantly going on in living cells lead to transformations of energy which find their final expression in the phenomena of life. The vital manifestations of the cell are, therefore, inseparably connected with physicochemic transformations, which require for their occurrence the existence of certain chemic and physical conditions.

Changes in the Cell Membrane.—Since most cells are in contact with surrounding fluids, they must be protected against changes of composition by a limited permeability of their surface layer, the cell wall or plasma membrane. This contains lipoid and protein constituents, and may be altered by fat solvents or by agents which either precipitate or liquefy proteins. This explains, at least partly, the effects of *lipolytic narcotics;* hemolysis by these, by *alkalis* and *saponins*; the actions of various *ions*; especially Ca, etc.

Osmotic Changes.—Cells are generally much more permeable to water than to dissolved substances. This leads to osmotic phenomena—the withdrawal or absorption of water—when the cells come into contact with solutions of higher or lower salt concentration. This explains the actions of many otherwise nearly indifferent salts, *e. g.*, *saline catharsis* and *diuresis.*

Surface Forces.—The physical structure of protoplasm is such as to present large surfaces and give peculiar opportunity for the development of surface forces, which are important for various vital functions. These are greatly modified by a variety of substances, including the *lipoid solvents, salts,* etc.

Colloid Phenomena.—Many chemical and physical conditions depend on the colloid character of protoplasm. The aggregation of colloids and their reactions are easily modified, especially by salts, acting by their chemic properties and electric charges. This is an important element in *salt action.*

Dependence of the Pharmacologic Action on the Chemic Constitution.—Drugs of different constitution may have apparently identical actions, as strychnine and tetanus toxin; arsenic and cholera infection; digitalis and barium; but the resemblance may be superficial. In general, however, drugs having a similar constitution possess similar actions; and definite changes in the molecule—as in homologous series, or the introduction of new groups—often produce definite modifications in the pharmacologic effects. This should be expected, since the physical as well as chemical properties change with the constitution. This relation has a wide general application; but its application to details has been rather disappointing, because sufficient knowledge is lacking to take account of the numerous variables. The data which we possess were gathered empirically.

The Importance of the Chemic Radicals or "Side Chains."—A substance, to produce chemical pharmacologic actions, must be capable of combining with protoplasm and then of altering its properties. These two functions—combination and action (analogous to amboceptor and complement, P. Ehrlich)—may be united in the same group; but they may be distinct ("haptophore" and "toxophore" groups), so that one may be modified without the other. Often several groups are present which may enter different combinations under different conditions. It is evident that these may introduce great variations in the actions. Side chains generally do not themselves produce pharmacologic actions, but act indirectly, by altering the chemical and physical properties of the molecule, for instance, its solubility, penetration, lipoid partition, surface affinity, oxidation and reduction. A few configurations, however, are important in themselves; for instance, the curare-action conferred by quaternary structure.

Crum-Brown and Fraser, 1869, showed that a number of alkaloids (strychnine, atropine, morphine and its esters) on conversion into *quaternary salts* by methyl iodide lose more or less of their original actions and acquire curare actions; this is also possessed by quite simple quaternary iodides—for instance, tetramethyl ammonium iodide; and other elements, such as sulfur or antimony, may be substituted for the nitrogen.

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OBJECTIVES OF TREATMENT

Physiologic functions tend to run their normal course, that being their most stable equilibrium; or to return to it when they have been disturbed by disease, either by "homeostasis" or by special reactions, as in inflammation. This constitutes the "*vis medicatrix naturae*," the healing power of nature. Adverse conditions may impede the tendency to normal, and the purpose of therapeutics is essentially to remove adverse and to establish favorable conditions for normal functioning.

Preventive or prophylactic treatment aims to protect the body from disease. It comprises individual and community hygiene.

Etiologic, Causal or Curative Treatment.—The cure of disease is scarcely possible while the original cause persists. If the cause can be discerned and removed, the conditions will generally return to the healthy normal unless anatomic lesions have already occurred. The chances for complete recovery are therefore the better, the earlier effective treatment is instituted. Even considerable anatomic deficiencies, however, can be compensated by the fact that the organism has large "factors of safety" (Meltzer).

Symptomatic, Functional or Alleviative Treatment.—When the cause of the diseased condition can not be attacked, it is often possible to remove its functional manifestations or symptoms. This may be useful in some cases, objectionable in others.

The symptoms in themselves may be so objectionable or lead to such secondary results as to make their removal desirable. Pain, cough and fever are symptoms, but they may require relief even though the root of the disorder may not be removed. The derangement of function may be immediately dangerous, as cardiac dilatation; or it may add to the tax on the diseased organs, as the edemas of valvular disease. Faulty functionation may also be relieved by increasing other compensating functions, such as diaphoresis in renal disease. On the other hand, the symptoms may be deceptive—a febrile chill may not require external heat; a referred pain may not be relieved by application of a local anesthetic to the place where it is felt. Removal of the symptoms may remove the index to the treatment of the underlying disorder. In many cases the symptom may itself be salutary, as cough when there is hypersecretion of mucus; or pain when rest is indicated in fracture.

Restorative or Roborant (Strengthening or Tonic) Treatment.—Disease generally impairs the vitality and resistance of the organs directly involved, and of the body at large. This is corrected by rest and efficient nutrition of the diseased organs and of the entire patient; and by correcting any other abnormal conditions (digestive disturbances, suppurations, etc.) which may be present, and which are drains on the vitality of the patient.

Expectant treatment is the absence of treatment beyond hygiene, rest, diet and other similar general measures, with the object of leaving the powers of nature free play. It should be employed in all cases where no better treatment is known. Expectant treatment must be used when it is desired to let the disease progress to a certain point for diagnosis.

Empiric and Rational Therapeutics.—The treatment of disease has developed by two different methods or, perhaps more accurately, attitudes of mind. The *empiric* method follows the dictates of apparent experience, without concerning itself about the reasons of these. It is typified by the charlatan slogan, "It has cured others and will cure you." The objection to the empiric method is not that it rests upon experience, for this is the basis and final arbiter of all science, but that it does not endeavor sufficiently to distinguish whether the experience is real or deceptive, whether the analogy is superficial or genuine. It is an equally grave error to base treatment on theories and deductions inadequately supported by observation. *Rational or scientific therapeutics* should employ observation, experiment and scientific reasoning, checking each against the others.

Pharmacal and Nonpharmacal Therapeutics.—A distinction is sometimes made between "drugs" and "physiological agents," including under the latter physical measures, such as heat or cold, bathing or climate, rest, exercise and massage, diet, etc. The distinction is convenient, but not fundamental. The use of drugs is no more "unphysiological" than the use of abnormal heat or cold, or of special diets. The mechanisms of their action are not essentially dissimilar. Each is intended to produce definite changes of functions. One or the other may be better adapted to secure this end. The body normally produces a variety of pharmacologically active substances, as direct or by-products of its metabolism, and uses them as aids in regulating its own activity. The CO_2 control of the respiration and the various hormones and internal secretions are familiar examples in mammalian physiology (Starling, 1908).

The historical evolution of the treatment of disease explains many errors which still adhere to the subject. Primitive man attributed disease to malevolent spirits which could be appeased by prayers and incantations. This formed the principal "medicine" of prehistoric ages, as it does of the modern savage. It survives in a modified form in "Christian Science." Chance and the observation of animals revealed that certain material products are also efficient. When this was limited to actual observation, the results were usually good; but the fantastic, half logical incongruity of the untutored mind led to bizarre relations.

The Middle Ages tried to combine the spiritual and the material treatment. It was reasoned that the Deity alone could cure disease, but that He had given man material remedies, and had put a seal upon them by which man might know them. Thus arose the doctrine of "signatures," that the use of a remedy was suggested by a fanciful resemblance in shape or color to some organ; *e. g.*, the liverwort, the lungwort, bloodroot, etc. Even a name was sufficient. Silver was used in lunacy because it was dedicated to Luna. In the meantime, alchemists had arisen with their search for the philosopher's stone, which was to convert all metals into gold, and cure all diseases. They gave their nostrums extensive trial on sick and well. The school of spagyrists was founded toward the end of the fourteenth century and reached its zenith with Paracelsus. They insisted upon the mystical virtues of antimony, arsenic, silver and chemicals in general, and stood opposed to the Galenists, who used only organic drugs. Notwithstanding their mysticism, which savors of quackery, they discovered some valuable medicines. A mass of materials, rubbish and otherwise, was added to the various simples, etc. Having a well stocked armory, the physician of that day felt that he was not doing his duty unless he gave his patient the benefit of it all, and the "shot-gun" prescription flourished.

The Homeopathic Doctrine.—A reaction against excessive drugging set in, and had as one of its results the establishment of homeopathy by Hahnemann at the end of the eighteenth century. He believed that disease depends upon a perversion of the spiritual vital powers and is immaterial in its nature. Logically, a thing spiritual could not be combated by material remedies, and Hahnemann turned to a spiritual power which he believed to be bound up in plants and liberated by dilution. The activity would therefore increase with the dilution, and be the greater, the smaller the dose (*doctrine of potency*). He thought that this liberation of the principles exactly turned their action around, so that the action of his dilutions was, he stated, exactly the opposite of that of the concentrated drug, and could be used for the relief of such symptoms as the latter produced: *Similia similibus curantur*. This was the first tenet of Hahnemann. The second was that, the nature of the disease being unseizable, it was not subject to treatment, and only its symptoms could be treated. Hence homeopathy in its pure form had no place for the medical sciences, such as physiology, anatomy, pathology or chemistry. The claims of homeopathy as a rational system hinge on the proof of the *similia similibus* theory and of the doctrine of potentiation by dilution. Its adherents appear to be considerably divided on these questions (Boyd: "The Simile in Medicine," Boericke and Tafel, Philadelphia, 1936). Some seem to deny the relevance of scientific evidence, and to base themselves purely on the slippery ground of superficial experience. Others, while they neglect the bulk of scientific experience, avail themselves of such experimental facts as can be turned into a specious support. Hahnemann seems to have started from the observations that large doses of drugs produce the opposite effects from moderate doses. This holds true for some cases, but it does not warrant the assumption that infinitesimal doses must again cause increasing effects opposite to those of moderate doses! The discovery of the effect of dilution on ionization has been used as illustrating homeopathy, disregarding the fact that the majority of the substances employed in homeopathy are not electrolytes. Hahnemann accomplished considerable for medical science by calling attention to the importance of diet and hygiene, when these were too much neglected; but perhaps the principal use of homeopathy has been to emphasize that disease tends to recover even without medical interference.

Therapeutic Nihilism.—One of the passing fads of medicine was an almost total emancipation from all drugs. This dates from the establishment of the Vienna School by van Swieten in 1745. The strongest advocate of nihilism was Skoda (1805–1881). Such nihilism was perhaps necessary at that time. The accumulated refuse was so great as to bury the good; to discard the whole and to begin anew may have been the quickest way to progress. The dominant motive, however, was probably the absorption of interest by the then novelty of physical diagnosis, which tended to the neglect of the traditional duties of the physician: "sometimes, to cure; often, to relieve; always, to console."

The Rise of Rational Therapeutics.—The reestablishment of therapeutics, founded now upon reason, was eventually aided by the physical methods of diagnosis, for these made it possible also to demonstrate the effect of remedies. The isolation of active principles (led by the discovery of morphine in 1817) substituted definite for indefinite drugs. Finally followed animal experimentation, the foundation of modern pharmacology.

Many of the older therapeutic measures, both drugs and physical, have not stood the test of critical examination and have been abandoned or are less used. The same critical methods, however, have confirmed the value of other measures, and established that of new drugs, on a firmer basis. Even the surgeon, whose therapy is mechanical by definition, uses general and local anesthetics, hypnotics, sedatives and analgetics and various antiseptic and antibiotic agents; salines for collapse and for catharsis; tannic and picric acid for burns; radiopaque agents; iodine and thiouracil, thyroid and parathyroid, epinephrine and pituitary, atropine and physostigmine, insulin, vitamins, antisyphilitic therapy and many others.

Psychotherapy.—At the same time, the mystic has been further developed in the many forms of suggestion employed in its milder forms by every physician as "the personal influence" and the "faith in doctor and medicine." It often constitutes all there is of merit in those medical fads which have accompanied medical science.

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GENERAL TOXICOLOGY

Toxicology is the science of poisons. The details of the actions and symptoms will be considered in connection with the individual poisons, but certain matters of general application may be discussed here.

Definition.—A poison is any substance which, acting directly through its inherent chemic properties, and by its ordinary action, is capable of destroying life or of seriously endangering health, when it is applied to the body externally, or in moderate doses (to 50 Gm.) internally. This definition excludes injurious mechanical, physical and bacterial agents, which are not commonly classed as poisons. It also excludes substances which are injurious only in very large doses. This is somewhat arbitrary, as are all definitions (see, *f. i.*, the collection by Murray and Frame, 1914).

Etiology.—Poisoning may be classified as criminal, suicidal, industrial or accidental. The statistics for these vary from year to year. Suicidal poisons are likely to follow vogues.

The *incidence of fatal poisoning* in New York City for 1937 may be taken as illustrative. Exclusive of alcoholism and anesthetic accidents, it included 898 persons. Two-thirds of these deaths occurred from carbon monoxide. Next to this, the suicidal deaths were caused by cyanide, barbiturates and mercuric chloride; the accidental deaths by heroin, arsphenamines, methyl alcohol and barbiturates. Homicidal poisoning was rarely diagnosed correctly during life (M. Helpern, 1939). Some 1200 deaths from accidental poisoning occur annually in the United States. About a fourth of these are in young children, and of these about seventy-five are from strychnine, generally in cathartic pills; sixty are from methyl salicylate. Wood alcohol caused about 150 deaths (Metropolitan Life Statistical Bulletin, Feb., 1944).

Industrial exposure to toxic chemicals is of increasing importance. It is most effectively met by preventive measures; by minimizing opportunities for exposure and by eliminating unsuited personnel, individuals "below par" (J. M. Foulger and Fleming, 1941) and those with susceptible skin.

Symptoms of Poisoning.—*Suspicion of poisoning* is aroused if a person, previously in good health, manifests rather suddenly marked pathologic symptoms which rapidly become worse. The suspicion becomes more firm if the phenomena appear a short time after swallowing some substance which may perhaps have an unusual odor or taste, if they agree in character with those produced by some group of poisons, and if they do not agree with any other disease.

Symptomatic Classification of Poisons: The following classes are generally recognized.

1. *Irritants* produce inflammation; if they are taken by mouth, there is pain throughout the alimentary canal, vomiting, purging, delirium, coma. So many poisons are to some extent irritant that these symptoms are commonly present. The irritants can be subdivided into *corrosives*, which produce direct destruction of tissues, and *simple irritants*, which do not. If corrosives are taken by the stomach, the vomit is often bloody.
2. *Nerve poisons* act on the neuromuscular apparatus, and include most of the poisons which are fatal in minute doses. They are subdivided into: *Convulsants*, which cause spasms; *Somnifacients*, causing sleep and coma; and *Cardiac poisons*, which stop the heart.
3. *Blood poisons* alter the hemoglobin or blood corpuscles. These include the toxic gases, the nitrites, etc. Many produce cyanosis.

The actions of a poison are usually not confined to one class of structures or functions. All functions suffer directly or indirectly, and the final *cause of death* is arrest of the heart or paralysis of respiration, preceded by the phenomena of *asphyxia*. In virtue of the latter, or through other causes, the urine often contains sugar.

The duties of the physician in cases of poisoning are twofold: to save life or suffering, and to forward justice. The former object requires the removal of the poison, the administration of chemical antidotes and the treatment of the symptoms. *To detect the poison* and to aid in fixing the guilt on the proper person, the physician must observe the symptoms, take possession of any suspected material, medicine, vomit, etc., and in case of autopsy, preserve the stomach and its contents, the intestines and contents, blood, liver, kidneys and portions of other organs, *separately*, without antiseptics, in clean, hermetically closed glass vessels, which should be sealed with wax. An exact *written record* of all the observations should be made as soon as possible.

TREATMENT OF POISONING

Although every case of poisoning must be considered by itself, certain general principles are widely applicable. These are especially important when the nature of the poison is unknown. The rapid course of poisoning demands that whatever measures are taken, *must be taken quickly*. The physician should be thoroughly familiar with the general rules of treatment, so that no hesitation or delay occurs. The antidote nearest to hand should be used in preference to one which can be obtained only with delay, even if the latter should be theoretically preferable.

The treatment of poisoning is directed against the cause and the symptoms. The former consists in *removing the poison*, or in *rendering it harmless*. Since neither of these objects can usually be attained absolutely, both are generally attempted at once.

Removal of the Poison.—The measures vary with the site to which the poison was applied. *On the skin and on accessible mucous membranes* this is accomplished by thorough washing with water. which is also useful by diluting the poison. If the poison is only sparingly soluble in water (as phenol), alcohol may be employed. Soap may be useful, but should be avoided if the poison is an alkali. The appropriate chemical antidote may be added to the wash water (for acids or bromine: soap or sodium bicarbonate or borax or lime water; for alkalis: diluted vinegar or lemon juice). The chemical neutralizant must be sufficiently diluted so that it is not itself harmful. Further treatment of irritation consists in the application of oils or salves. If the poison has been applied *hypodermically or to wounds*, the systemic effects may be lessened by preventing or retarding the absorption of the poison. If the absorption can be delayed sufficiently so that the drug is excreted as fast as it is absorbed, doses which would otherwise be fatal may cause no effect. The best means for this purpose is a firm ligature applied centrally to the wound. Where this is not feasible, suction, cautery or excision may be practiced. If an irritant poison has been *taken by the mouth*, the oral cavity and the pharynx demand the same treatment as would the skin. With *gaseous poisons*, the treatment consists in free ventilation of the lung, using artificial respiration and oxygen, if necessary. Addition of 5 per cent of carbon dioxide hastens the ventilation.

Removal from the Alimentary Canal.—If the poison was taken by mouth, the stomach should be emptied by lavage or by an emetic, even though vomiting has occurred spontaneously, and even if the patient is not treated till several hours after swallowing the poison; for some poisons remain in the stomach for a long time. Contraindications are corrosion and advanced strychnine poisoning. These require judgment and caution. After the stomach has been evacuated, 15 to 30 Gm. of magnesium sulfate should be administered in water to clean the intestine of slowly absorbable poisons.

Evacuation of the Stomach.—Lavage has advantages over emesis. It cleanses the stomach more effectually, particularly of small undissolved adherent particles; it is less depressant to the patient; and it permits the effective use of chemic antidotes. It is indispensable with depressant poisons which paralyze the vomiting center, such as deep morphine or chloral poisoning.

The complicated stomach pump has been replaced by the more convenient stomach tube. In emergencies, 6 feet of rubber gas tubing, with a funnel attached, answers very well. The tube should not be *forced* down, but should be *gently* pushed to the pharynx, where the pharyngeal muscles will grasp it and push it further. Care should be taken to avoid overdistention of the stomach; it is better to use small quantities of fluid repeatedly. The chemical antidote may be added to the lavage water (for instance, potassium permanganate, 1:2000, against organic poisons), and 100 to 300 cc. of the antidotal solution should be left in the stomach at the end. If there is trismus, or the patient resists, the tube may be passed through the nose.

Emetics have the advantage of greater convenience, and avoid struggling. They should be repeated every fifteen to thirty minutes, if necessary. *Household measures* which may be used before the arrival of the physician include tickling the fauces with the *finger;* gargling with *soap suds; table salt,* a tablespoonful to a glass of warm water, repeated four or five times if necessary; and *mustard,* a teaspoonful stirred in a tumbler of warm water. *The most effective emetic* is *apomorphine,* 5 mg. (grain $\frac{1}{12}$), hypodermically. It is the only emetic which can be given by the skin, and is therefore particularly useful if the patient resists. It is prompt and certain, but rather more depressing than *cupric sulfate or zinc sulfate,* which act promptly and with a minimum of depression, but should not be given if the poison is a corrosive. Zinc sulfate is less irritant than the copper, and nearly as efficient; 2 Gm. may be given in a glass of water. The dose of copper sulfate is 0.5 Gm. at once, or three doses of 0.3 Gm., fifteen minutes apart. If it is ineffective it must be removed by lavage. *Ipecac,* a teaspoonful of the powder in water, or a tablespoonful of the syrup, is uncertain and produces considerable depression.

Hypodermically injected drugs cannot be removed effectively, but their absorption may sometimes be delayed by epinephrine or by a tourniquet, and this may greatly lower the toxicity by permitting excretion or destruction of the poison, or its fixation in the liver. Water should be administered freely to favor diuresis; but diuretics do not generally hasten the excretion of poisons materially (Hatcher, strychnine; Sansum, 1918, tetanus toxin).

Chemical antidotes are often effective locally and in the alimentary canal, but with few exceptions (such as nitrite in cyanide poisoning) they are useless after absorption. They either neutralize or destroy the poison; or precipitate it or envelop it in an impenetrable coating; or adsorb it so as to slow or prevent its absorption. Since these antidotes are hindered in their action by the presence of food, and since the precipitates are not quite insoluble, it is advisable to combine them with lavage or emesis, adding the antidotes to the wash water, or giving them in the interval between vomiting; they must be repeated frequently.

Antidotes which destroy the poison in the alimentary canal include, *against Acids:* Alkalis (burnt magnesia, soap, chalk, baking soda). *Against Alkalis:* Weak acids (vinegar, lemon juice). *Against Organic Poisons* (*Alkaloids, Glucosides, etc.*) and *Phosphorus:* Oxidizing agents, especially potassium permanganate, 0.15 Gm. or a penknife-point full to the tumbler, repeated as often as it is vomited; or for lavage, a liter of 1:2000. It should be strained so that no undissolved crystals are administered. It is quite irritant, and its efficiency is limited, especially by the presence of organic matter. In snake bite, powdered permanganate may be rubbed into the wound, after free incision. Hydrogen peroxide is a useful though less powerful oxidant. *Against Hydrocyanic Acid:* Permanganate, arsenic antidote, hydrogen peroxide, and thiosulfate of sodium ("Hypo"). *Against Formaldehyde:* Ammonium carbonate.

Precipitants.—*Tannic acid* (a teaspoonful in water, or very strong hot tea, ad libitum) tends to precipitate various metals, alkaloids and a number of other organic substances. It is not reliable, but is harmless and does not interfere with other treatment. It is chiefly useful as an adjuvant. The effect is increased by the addition of sodium acetate or bicarbonate, and diminished by alcohol and acids, since the precipitates are soluble in these media.

From the experiments of Kiefer (1892) on tannic acid, and Sollmann (1901) on tea, these would be *useful* against: apomorphine, cinchona alkaloids, hydrastine, strychnine, veratrine, digitalis, antipyrine, colchicine and the metals: Pb, Ag, Al, Co, Cu, Ni, Ur, Zn, Fe. *Scarcely useful* against: cocaine, brucine, aconitine, lobeline, nicotine, pilocarpine, codeine, muscarine, physostigmine, solanine. *Practically useless* against: atropine, coniine, morphine, As, Sb, Hg.

Of other *specific precipitants,* the following should be remembered: For *alkaloids:* tincture of iodine, 15 drops in half a glass of water. For *metals* (especially mercury): raw eggs. For *mercuric salts:* sodium thiosulfate; sodium formaldehyde sulfoxylate. For *arsenic:* arsenic antidote (see Index). For *barium:* sulfates (Glauber's or Epsom salt). For *oxalates:* calcium (limewater, chalk, whiting). For *phosphorus:* cupric sulfate or oxidized (old) turpentine. The former envelopes the phosphorus with an insoluble coating of metallic copper.

Adsorbents act promptly to delay the absorption of many substances, and are harmless in any case. The most effective is "*activated charcoal,*" a tablespoonful in water, before and again after emptying the stomach. *Demulcents* (raw eggs, boiled starch, flour, milk) hinder absorption less effectively than charcoal, but they are useful if this is not promptly available. They also allay local irritation.

Symptomatic Treatment.—The symptoms produced by poisons can often be lessened or removed by the use of drugshaving an opposite action. These *physiologic antidotes* may not abolish the action of the poison, but only mask its symptoms. By tiding the patient over the dangerous period, and by preventing exhaustion, they may save life. Large doses of the antidotes often cause effects similar to those of the poison, which may add to the fatality of the latter. They must therefore be used in a ppropriate small doses. Themeasures which are generally useful are directed, in the *order of their importance*, to: supporting the respiration, heart and vasomotor tone; to lessen cooling, pain, convulsions and coma.

Respiration is usually the first function to fail, and this accelerates the other actions of the poison through the convulsant and paralytic effects of asphyxia. It is advisable to begin with the supporting measures as soon as the respiration shows signs of weakening. The measures consist in direct or reflex stimulation of the respiratory center; in artificial respiration; and in the administration of oxygen. *Reflex stimulation of the respiratory center* is the quickest, but can not be kept up as long as the direct stimulation. It may be secured by inhalation of ammonia water or smelling salts, or by aromatic spirits of ammonia (half a teaspoonful in a glass of water); the alternate application of heat and cold (slapping with wet towels); friction with alcohol; mustard plasters; faradization. *Direct stimulation of the respiratory center* is generally accomplished most effectively by inhaling 5 per cent carbon dioxide in oxygen. Other stimulants (lobeline, nicotine) require dangerous doses to be effective. Caffeine as such or as strong hot coffee, ephedrine and atropine are not very successful. The respiration may also be raised by improving the circulation. Saline infusion is useful. *Artificial respiration* should be employed when these measures are ineffectual. Excessive artificial respiration is likely to induce apnea, so that the patient does not breathe spontaneously because there is not enough CO_2 in the blood to stimulate the respiratory center. If the heart is strong, the artificial respiration should therefore be intermitted occasionally for a short time. *Oxygen* is useful if an asphyxiant gas is the cause of the poisoning.

Circulation.—It is sometimes possible to improve a failing heart by reflex stimulation, by the inhalation of diluted ammonia, by swallowing the aromatic spirit of ammonia, or by intravenous injection of normal saline solution, perhaps with the cautious addition of epinephrine (1:100,000). Lowering the head and bandaging the extremities also add to the blood supply of the brain and heart. Strychnine and atropine are generally ineffective. If a heart has been arrested through asphyxia, rather than through a direct cardiac action of the poison, and if it has not stopped longer than a very few minutes, it may sometimes be resuscitated by cardiac massage, combined with epinephrine by intravenous or, more effectively, by intracardiac injection.

Cooling is prevented by the application of external heat; **pain** by morphine; **convulsions** are controlled by the cautious inhalation of chloroform; **coma** by reflex stimulants, coffee and atropine.

Methods of Administering Antidotes.—Physiological antidotes should be given hypodermically or intravenously, if possible. This obviates the loss of the antidote through vomiting, and the response is prompter and more certain. If the circulation is low, the absorption of hypodermic injections may also be slow. It is therefore well thoroughly to massage the site of the injection, and if the circulation has almost stopped, to employ vigorous rapid rhythmical compression of the heart.

Résumé of the General Treatment of Poisoning.—Promptness is of vital importance. The physician should be familiar with antidotes; he should have these antidotes readily accessible; he should plan his treatment on his way to the patient. If he finds the condition of the patient dangerous, he should at once proceed to relieve the symptoms. Otherwise he should first administer the chemical antidote and evacuate the stomach;

apply heat; attend to the respiration, to pain, to any other symptoms; give a cathartic.

Antidotes for First Aid.—Every physician (and every drug store) should keep the following antidotes together, in a special satchel ("Antidote Bag") so that they can be readily transported. The dose should be written on each container. Amyl nitrite pearls; Apomorphine tablets, 2 mg.; Atropine tablets, 1 mg.; Bicarbonate of sodium; Caffeine-sodium benzoate; Charcoal, activated; Chloroform; Cupric sulfate, powdered; Epinephrine tablets, 1 mg.; Limewater; Magnesia, calcined; Metrazol, ampuls of 1 cc. of 10 per cent; Morphine sulfate tablets, 10 mg.; Nitrite of sodium, ampuls of 10 cc. of 2 per cent; Olive oil; Pentobarbital sodium, ampuls, 0.5 Gm.; Potassium permanganate, 1 per cent solution (to be diluted twenty times); Sp. Ammon. Arom.; Tannic acid; Thiosulfate of sodium, ampuls of 10 cc. of 30 per cent; Tr. iodine; Whisky; also a hypodermic syringe in good order, and stomach tube with funnel. The following may be demanded at the house of the patient: Boiled water; Coffee (strong, hot, and black); Eggs; Hot-water bags; Milk; Mustard; Salt; Soap; Starch, boiled; Tea; Vinegar. An interesting exposure of the contents of the *"doctor's bag"* is given in the Cornell Therapy Conference, New York State Journal of Medicine, August 1, 1943.

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MEDICINAL FOODS

These may be useful as adjuvants to other foods, for superalimentation; when digestion is low, as in fevers or convalescence; or to tide the patient over a temporary crisis; and in the feeding of infants.

Rectal feeding would be desirable when the stomach does not retain food or when food by mouth is inadmissible for other reasons, but its practical possibilities are limited mainly to dextrose, water and salt. It suffices only for short periods, depending on the previous condition of the patient, especially the adipose tissue. The rectum and large intestine have practically no digestive power, except to a limited extent for carbohydrates. Water, dextrose and sodium chloride are absorbed effectively from nutrient enemas. Dextrin is easily digested and then absorbed. Amino acids are absorbable, but proteins are not; not even peptones unless they are first broken down by bacterial putrefaction. Fats are practically unabsorbed.

The absorption of *water* is a normal function of the colon, for this resorbs one-half to two-thirds of the water of the colon contents. The entire water needs of the organism can be supplied by this channel, provided that the injections do not contain irritant substances and are not too strongly anisotonic. Many *salts* are absorbed perfectly, including NaCl. The colon expels hypo- and especially hypertonic solutions; 0.8 to 0.9 per cent NaCl is osmotically indifferent, but may cause thirst; 0.6 to 0.75 per cent is the best concentration. The most useful *carbohydrates* are dextrose (Bergmark, 1915) and dextrin, which are both absorbed. *Dextrose* may be used as 6 to 7 per cent for single injection, or 5 per cent for continuous irrigation. If salt is added, the dextrose must be reduced (for instance, 2.2 per cent of dextrose and 0.45 per cent NaCl). *Dextrin* is nonirritant in any concentration, and is easily digested. It may be used as 10 to 15 per cent for continuous irrigation; or 20 to 25 per cent for single enemas. This higher concentration makes it possible to introduce more calories than with dextrose. *Levulose and maltose* excite peristalsis. *Lactose* is not easily absorbed, and *galactose* is poorly utilized. *Saccharose* is absorbed poorly. *Starch*, boiled or raw, is nonirritant, and is somewhat digested, but only in limited quantity.

Proteins must be broken down to amino acids and polypeptids before they can be utilized. The colon readily absorbs these cleavage products, but its peptolytic power is insignificant. Bacterial putrefactive processes are active, however, and through them a fair amount of protein becomes absorbable. *Witte's peptone* may be given as 15 to 20 per cent in single enemas, or 5 to 10 per cent for continuous irrigation. About 75 per cent of its nitrogen is absorbed. Absorbable protein cleavage products can also be secured by pancreatin-digestion of milk carried on for twenty-four hours (Reach, 1901). This may be used as the vehicle for the dextrose (Bywaters and Short, 1913). Practically no protein is absorbed from milk or eggs unless they are predigested to the amino acid state (Bergmark, 1915; Adler, 1915).

Fats.—Only small quantities are absorbable from the colon (Makashima, 1914; Ornstein, 1918); at most 10 Gm. per day. Ordinary oils, such as olive oil, are least absorbable; milk and cream are somewhat better. Egg yolk is absorbed most efficiently, but is liable to putrefaction.

Alcohol is readily absorbed. Three per cent solutions are nonirritant; higher concentrations may be expelled.

Nutrient enemas may be given as "single enemas" or as "continuous drop enemas." With *single enemas*, two should be administered daily, each of 300 cc. They are warmed and injected very slowly through a funnel and soft rectal tube, inserted about 3 inches. The patient remains recumbent for at least two hours, and the anus may be compressed with a warm towel for ten minutes. Small enemas are carried by antiperistalsis to the cecum, but not into the ileum; with larger injections, some of the material passes into the small intestine (Cannon). With nutrient enemas containing albumen, peptone or fat, two cleansing enemas should be given daily; if only carbohydrate and albumen are used, one cleansing enema suffices. *Continuous drop irrigation is preferable.* The usual daily dosage is 1200 to 1500 cc., and not over 2 liters. Nitrogenous and carbohydrate injections are best given separately.

Parenteral alimentation is feasible for water, salt, and dextrose. These may be injected subcutaneously or intravenously when absorption from the alimentary tract is defective, as in acute fevers or shock. Proteins other than homologous plasma are unsuitable for parenteral administration, since they provoke toxic reactions. The injection of amino acids has given good results. Oil is but little absorbed from subcutaneous injection, and it is doubtful whether this is in suitable form for metabolism (van Noorden, 1920).

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DIGESTIVE FERMENTS

The digestion of food in the alimentary canal is accomplished mainly by the secretion of organic ferments or enzymes whose presence accelerates chemical changes. They are of enormous importance in the body, but of little practical importance in therapy. Commercial ferments consist of the dried gland, or more or less purified extracts, rich in protein, and dried or preserved by glycerin. The principal ferment preparations are: pepsin, papain, the diastases (malt) and pancreas. The term "fermentation" is derived from *fermentum*, leaven; and this probably from *fervere*, to boil. It was originally applied to all effervescence.

Several enzymes have been isolated as crystallized proteins; some have a prosthetic group, but proteolytic enzymes do not. Active enzymes may be formed from inert proteins by change of temperature or *p*H, by simple hydrolysis, by catalysis with other enzymes, or by autocatalysis, resulting in relatively slight internal rearrangement or rupture of the peptide link (review, J. H. Northrop, 1937). Cleavage ferments may produce syntheses under proper conditions.

Conditions of Action and Deterioration.—The digestive ferments are specifically adapted to the hydrolytic cleavage of the various food products (amylolytic, proteolytic, lipolytic, etc.). Their activity is influenced by various conditions, especially by temperature (40° to 45° C. being optimal for mammalian ferments); by acid or alkaline reactions; by salts, etc. Solutions are unstable. They are destroyed immediately by boiling and more gradually by any excessive conditions, and by putrefaction.

Pepsin is much more resistant to destruction than trypsin, but both deteriorate even in neutral solutions, trypsin often in a few days. Even dry "pancreatin" is unstable (Long and Muhleman, 1914). Pepsin can be completely destroyed by shaking (Shaklee and Meltzer, 1909). Solutions of ferments are *incompatible* with excess of acid and alkali (Long and Muhleman, 1914) or salts; with many antiseptics; with excess of alcohol; and with all protein precipitants. Pepsin in neutral or alkaline solution is destroyed by sodium chloride (W. H. Hamburger, 1915).

Mixtures of ferments digest each other more or less rapidly according to their reaction. Pepsin, in the presence of weak acids, destroys trypsin and amylopsin completely; but trypsin has little effect on pepsin under ordinary conditions (Long and Muhleman). "Compound Digestive Elixirs," supposed to contain pepsin with pancreatin, etc., are practically worthless (J.A.M.A., *48*:434, 1907).

The administration of ferments in digestive disorders has not realized the early expectations (Bastedo, review, 1925). Digestive disturbances are rarely due to deficiency of ferments, and it is difficult to administer ferments so that they can develop their actions.

Persistence of Ferments in the Stomach.—The reaction of the stomach is best suited to pepsin, and is more or less inimical to diastase and trypsin. But when these ferments are thoroughly mixed with food, they may act in the fundus of the stomach for an hour or so (Cannon), before the mass becomes acid (Gruetzner, 1905); and since the acid is largely bound by the proteins, some of the trypsin may pass the stomach unchanged (Long and Hull, 1917). The actual quantity is generally too small for any practical use. The action of papain is too feeble at body temperature to deserve consideration.

Other Uses.—A more rational field for ferments is in the preparation of predigested foods, especially for rectal alimentation, but these also are of little use. **Pepsin and rennin** are employed for curdling milk. Pepsin has been used to dissolve diphtheritic membranes, and as a dressing for fetid ulcers (as mentioned by Wm. Beaumont for gastric juice). *Desiccated stomach* contains an agent which acts on meat to form the "antianemic principle" (see Index), but this is not present in pepsin or other digestive extracts of the stomach.

Pepsin is a proteolytic extract obtained from the mucous membrane of the stomach of the pig, sheep or calf. Solutions deteriorate readily and are incompatible with alkalis, salts, metals and tannins; acid solutions deteriorate gradually in proportion to their acidity. Pepsin is most active in acid solutions of about *p*H 2. Dose, 0.5 Gm., 8 grains.

Liquid Rennet (Liq. Seriparus) consists of extracts of the fourth stomach of calves; used to coagulate unboiled milk (1:100 to 300, 38° C., 100° F.) for the preparation of junket and whey.

Pancreatin, U.S.P., is generally dried pancreas, but is defined as a substance containing enzymes, principally pancreatic amylase (amylopsin), trypsin, and pancreatic lipase (steapsin), obtained from the fresh pancreas of the hog or ox. It converts not less than twenty-five times its own weight of starch into soluble carbohydrates and not less than twenty-five times its weight of casein into proteoses. Lipase is often absent, since it is destroyed by trypsin, which is a collective term for a series of proteolytic enzymes (Northrup, 1937). The amylopsin acts best in a faintly alkaline (0.025 per cent $NaHCO_3$) or neutral medium, and is destroyed by very weak acidity (0.006 per cent HCl) (Long and Muhleman, 1914). Trypsin also is most potent when alkaline (0.2 to 1 per cent Na_2CO_3) but is somewhat active with very weak acidity. The optimal reaction varies for different proteins (Long and Hull, 1917). Excess in either direction is detrimental. It acts best on fibrin or casein, feebly on cooked albumen, and scarcely at all on raw albumen (Long and Muhleman; Sugimoto, 1913). Pancreatin occurs as a cream-colored amorphous powder having a faint, peculiar odor. Slowly sol. in water; insol. in alc. Dose, 0.2 to 0.6 Gm., 3 to 10 grains.

Hypodermic trypsin injections against cancer were advocated by J. Beard, 1905, and Shaw-Mackenzie, 1906, but proved disappointing. They produce local lesions and toxic effects resembling peptone poisoning (Wago, 1919). *Papain* and *takadiastase* act similarly (Kirchheim, 1913). *Intravenous injection of trypsin* is very toxic (W. Hildebrandt, 1890), producing acute symptoms similar to anaphylaxis, even when crystallized preparations are used (Rocha e Silva, 1939; with Dragstedt, 1941). Unanesthetized dogs respond with vomiting, urination, defecation and collapse. Anesthetized dogs show prompt and profound fall of blood pressure, congestion of the liver and viscera, and increase of histamine content of the blood. The blood becomes noncoagulable, probably through heparin. Guinea pigs develop acute pulmonary embolism, with collapse of the lungs instead of the distention of true anaphylaxis. The effects are not due to digestion of the blood or tissues, for they occur within a few seconds. Heat inactivates the trypsin, and repeated injections of small doses desensitize. Animals that recover develop hepatitis and renal damage similar to burns and crushing (Mirsky and Freis, 1944). Excised uterus and intestines are strongly contracted by addition of trypsin to the bath; this effect is inhibited by arginin (Dragstedt and Wells, 1944).

Fresh pancreas also contains *insulin*, but this is easily destroyed and is not present in "pancreatin" or in ordinary extracts, nor does it pass into the pancreatic juice. Excision of the pancreas causes fatal diabetes, which may be prevented by the administration of insulin. Nevertheless, the animals die after some months, with extensive fatty infiltration and degeneration of the liver. This may be prevented and cured by feeding raw pancreas or a substance "*lipocaic*" extracted from it (L. R. Dragstedt *et al.*, 1936, 1940). Choline also furnishes some protection (Best), as does methionine. Lipocaic is fully effective, although its methionine and choline content are below their own effective level (D. E. Clark *et al.*, 1945). It has been reported as curing some obstinate cases of psoriasis, but this requires confirmation.

Papain is the dried milk juice of the unripe fruit of the "melon tree," Carica papaya. It converts proteins to amino acids in acid and neutral media (*p*H 4 to 7), but it is more variable and less active than pepsin. Its optimum temperature is 80° to 95° C. Dose, 0.1 to 1 Gm. Its chief use is in the preparation of "tenderized meat."

Diastatic ferments are obtained from malt and other sources; "takadiastase" is prepared from a Japanese mould. The therapeutic value of these preparations is questionable, as their action is weak and unreliable, and much better results can be secured by managing the diet. *Malt* is the grain of barley, Hordeum vulgare, partially germinated, and dried at a temperature not exceeding 55° C. *Extract of Malt* is prepared by extracting the malt with water at 60° C., evaporating at this temperature, and preserving by the addition of glycerin. It is a viscous, light brown liquid, sweet, has an agreeable odor, and is capable of converting not less than five times its weight of starch into water-soluble sugars. Dose, 15 Gm., 4 drachms.

Lactic acid-producing organisms were introduced by Metchnikoff, with the idea of acidifying the intestines and thereby preventing intestinal putrefaction, which he held responsible for premature senility. This theory of old age was without scientific support; nor does the administration of the organisms advocated by him (Bacillus bulgaricus) or of milk soured by them, check intestinal putrefaction. They succumb promptly to the ordinary putrefactive bacteria of the intestines. The growth of B. acidophilus, which is normally present in the intestines, can apparently be increased by administration of its culture. *Sour milk* is sometimes beneficial, especially in pediatrics, against vomiting, acute and chronic diarrhea, tc., and there are advantages in souring the milk by Ba. ecidophilus cultures.

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PROTEIN FOODS AND AMINO ACIDS

Protein foods provide the *amino acids* which are used in the construction of the tissues. Some of these cannot be adequately synthesized in the body, and are therefore essential food constituents. They are liberated during digestion and pass unchanged into the portal circulation. Mixtures of purified amino acids can largely take the place of protein foods (review, W. C. Rose, 1938); but growth of mice and rats is less than when native protein, such as casein, is added (D. W. Woolley, 1946; Womak and Rose, 1946). On the basis of analogous phenomena with certain bacteria, the deficiency is attributed to the absence of an unidentified factor, "strepogenin," which is present in many proteins, including casein, but not in egg albumen or gelatin. It is not an amino acid, nor any known vitamin (Sprince and Woolley, 1944).

Isotope studies of protein metabolism show that most tissue proteins are constantly undergoing synthesis and degradation, so that more than half of the protein of the liver, for instance, is replaced in ten days (Borsook and Dubnoff, 1943). This involves rapid shifts in the amino acids (review, Schoenheimer and Rittenberg, 1940).

Meat and Beef Juices, when prepared extemporaneously by expression of fresh or slightly broiled meat, contain from 2.5 to 9 per cent of coagulable proteins, and 2 to 4 per cent of other proteins and nitrogenous extractives. They have a moderate value as sources of nitrogen. The commercial preparations are supposed to be concentrated; in fact, however, they are inferior, containing but 0.2 to 3 per cent of coagulable proteins; others are reinforced by the addition of defibrinated blood, sugar, glycerin, etc., which are of doubtful utility (Rep. C.P.C., J.A.M.A., Nov. 20, 1909).

Bouillon (beef tea) is prepared by boiling meat with water; the *meat extracts* by evaporating the solution to a semisolid consistency. The coagulable proteins are removed by this process, the extract containing the salts of the meat, the flavoring substances and meat bases (xanthine and creatine products) and noncoagulable protein, in the form of gelatin, albumoses, etc. In the small amounts in which they are used, these preparations contain a *very insignificant quantity of nutriment.* They are *valuable as stimulants.* They owe their action largely to the odorous principles they contain, which are excellent stomachics (Wolff, 1912). American brands of the Liebig (pasty) type of meat extract contain, on the average: flesh bases, 26.4 per cent; gelatin and albumose, 16.5 per cent; N-free extractives, 14.6 per cent; inorganic salts, 22.5 per cent; water, 20 per cent (N.N.R., 1920). *Dry "peptones"* are the dried product of the artificial digestion of meats, usually consisting mainly of albumoses. Their taste is disagreeable and they often cause irritation. Peptones stimulate pancreatic secretion more effectively than acid or secretin (J. E. Thomas and Crider, 1941). Intravenously they are toxic, lowering the blood pressure and rendering the blood noncoagulable (see Index).

Hydrolyzed protein foods have only a limited field in oral therapy, for instance in allergies; but they have an important place in parenteral nutrition. Their usual base is casein. Acid hydrolysis destroys the tryptophane, and synthetic tryptophane is added at the end. Enzyme hydrolysis (by pancreas) does not destroy any amino acid, but it may not break down the protein completely. Alkali hydrolysis is unsuitable, for it destroys methionine and cystine and converts other amino acids into their racemic form.

Intravenous protein nutrition, with nitrogen balance and plasma protein restitution, may be achieved in man as well as in animals by injection of compatible plasma or, more safely and conveniently, of mixtures of protein hydrolysates containing the essential amino acids administered by vein, hypodermically or by mouth (Henriquez and Anderson, 1914). It is useful to offset serious loss of protein in severe burns, wounds, surgical procedures and infections (review, R. Elman, 1945).

Toxic effects occur only if the digestion has not gone far enough to split all true protein; small peptide molecules are not dangerous. Vomiting may be produced by *glutamic acid* above 100 mg. per Kg. of body weight, especially if it is injected rapidly. The other amino acids do not cause symptoms even with 300 mg. per Kg. (S. C. Madden *et al.*, 1945). Mild nitritoid reactions may be avoided by injecting slowly. The addition of 10 per cent of dextrose, however, produced phlebitis in dogs (Howitz *et al.*, 1943). Strict technic should be observed.

Aminogen is a commercial enzymatic hydrolysate of casein and pork pancreas. It is well utilized and adequate. No serious reactions have been reported, and no fever if it is properly prepared. A 5 per cent solution in 5 per cent dextrose neutralized with NaOH to *p*H 6.5 contains 0.5 per cent of NaCl. It should not be injected more rapidly than 500 cc. per hour, to 1.5 or 2 liters per day. Faster injection causes nausea or vomiting. An enzyme digest of casein with added tryptophane and cystine has also been employed successfully (Altshuler *et al.*, 1940).

Amino Acid Deficiency.—Osborne and Mendel, 1912, showed that animals cease to grow if placed on diets deficient in one of the essential amino acids, such as lysine or tryptophane. *Lysine deficiency* in rats also produces vascularization of the cornea (C. H. Hock *et al.*, 1945). Protein deficiency results in massive acute *necrosis of the liver,* differing fundamentally from the acute zonal necrosis of liver poisons. *Methionine* gives complete protection (Glynn and Himsworth, 1944). It also protects against dietary fatty liver (D. E. Clark *et al.*, 1945). Synthetic *dl*-methionine (*meonine*) is available in tablets of 0.5 Gm. for the clinical prophylaxis (0.5 to 1 Gm. daily) and treatment (1.5 to 3 Gm. daily) of liver injury (Report, Council on Pharmacy and Chemistry, 1946, J.A.M.A., *132*). If the food is partly deficient in a constituent, this is not easily compensated by increased food consumption; for the appetite is regulated by the energy requirements, and not by the growth requirements. However, this phase of food deficiency probably does not occur easily under the practical conditions of civilized life. Further work, especially by W. C. Rose (reviews, 1937, 1938), has shown that only ten amino acids need be supplied as such by the food: arginine, histidine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophane and valine. The others can be synthesized from these more or less readily as needed. Man can synthesize all but eight (W. C. Rose *et al.*, 1942). The indispensability varies with age; for instance, adult rats can synthesize adequate arginine, but young rats need an outside supply (Scull and Rose, 1930). Deficient income of certain of the amino acids (lysine, methionine, cystine, glutathione) inhibits the growth of mouse tumors, as well as the growth of the animal (C. Voegtlin *et al.*, 1936, 1937). Topical application of an amino acid mixture accelerated the healing of *corneal wounds* (A. J. Schaeffer, 1946).

The "dynamic action" of proteins, i. e., the increase of heat production caused by their ingestion, is the sum of the actions of their amino acids; phenylalanine and tyrosine have the greatest effect, valine and histidine have none (Rapport and Beard, 1927, 1928). Some amino acids, including synthetics, favor the *formation of hemoglobin* (Whipple, 1938).

Amino-acetic acid (glycocoll, glycine), $CH_2.NH_2.COOH$, unites with benzoic acid to form hippuric acid. It was reported to produce improvement of muscular strength in myasthenia gravis when administered continuously in large doses (10 Gm., two or three times daily, usually in milk). The action was attributed to conversion into creatine, which is important in muscular metabolism (Milhorat *et al.*, 1932 to 1934; P. Wolff, 1935). The response was variable, however, and further experience has been disappointing, so that it is but little used, especially since neostigmine has proved much more satisfactory. In normal subjects it has no effect on muscular capacity, nor does it increase the normal creatine or creatinine excretion (although it had been reported to raise it markedly in muscular dystrophies). The ordinary diet furnishes ample supplies of amino-acetic acid, and 13 to 17 Gm. can be synthesized from the ingested proteins (review, L. Young, 1939). It constitutes about 25 per cent of gelatin (King, McCaleb *et al.*, 1942; Horvath, Knehr and Dill, 1941).

Amino-acetic acid is soluble in water. Average dose, 30 Gm.

Creatine plays an important role in the phosphate metabolism of muscular contraction and of nerve stimulation; about 98 per cent of the total creatine is found in the muscles as creatine-phosphoric acid (phosphocreatine). Administration of radioactive phosphate or radioactive creatine shows rapid formation of phosphocreatine in the muscles, and a rapid turnover in muscular work. It also shows the conversion of body creatine into urinary *creatinine*, the form in which it is excreted (1 to 2 Gm. per day) after losing an H_2O molecule (Bloch and Schoenheimer, 1939). Once formed, creatinine does not reenter metabolism; practically all that is absorbed is excreted unchanged (R. Dominguez and Pomerene, 1945). *The urinary output of creatine is* increased most markedly by the administration of glycocyamine; next comes amino-acetic acid, but this requires ten to twenty times as much; alanine is still less effective; histidine and glutamic acid have generally no effect; choline and guanidine are quite ineffective (Bodansky, 1936). Creatine excretion is increased by acid-producing foods (oats and corn) and diminished by base-producing foods (carrots). It is increased by carbohydrate deficiency and by starvation (Underhill, 1916). *The blood sugar level* of fasting dogs is lowered by the hypodermic or oral administration of creatine, but not to the convulsive level (R. M. Hill and Mattison, 1929).

Glutamic acid, $C_3H_5(NH_2)\ (COOH)_2$, alpha aminoglutaric acid, occurs as a constituent of the protein, and also free in certain tissues and in blood plasma (6 to 10 mg. per 100 cc.), in the white and yolk of eggs, and in many plants, such as beets. It is apparently related to carbohydrate metabolism, its blood concentration being diminished by insulin and by glucose administration. It is not toxic and is used to impart meat flavor to foods (M. M. Harris, Roth and Harris, 1943). It was tried in place of amino-acetic acid in muscular dystrophy, but with discordant results (R. B. Gibson, 1934; Tripoli and Beard, 1934). *Glutamic acid hydrochloride* was suggested by L. B. Mendel as a possible means of administering acid in solid form to aid gastric digestion, but it was found to hinder digestion *in vitro* (Report of Chem. Lab. A.M.A., 1937).

Tryptophane (indol amino propionic acid) deficient diets fed to young rats for eight to eighty-two days produce *cataract*, corneal vascularization, loss of weight, greasy hair, alopecia and nervousness. The cataract differs from that resulting from riboflavin deficiency or from feeding galactose or xylose (Trotter and Day, 1942).

Tyrosine (p-hydroxyphenyl-alpha-propionic acid), if 10 per cent is added to the diet of rats for one or two weeks, produces purulent keratitis, swelling of the feet, degenerative changes in the pancreas, kidneys and arterioles, ending in death within five weeks (Hueper and Martin, 1943).

Gelatin, a partly hydrolyzed protein, is a fairly useful food in the form of soups and desserts, but is deficient in some of the essential amino acids, notably tryptophane, valine and tyrosine, so that it can not replace more than one-fourth to two-thirds of the protein of the ordinary diet (Murlin, 1907). Gelatin dessert powders contain only about 10 per cent of gelatin.

Gelatin was suggested as a *source of amino-acetic acid* in myasthenia gravis, but to supply the ordinary daily 20 to 30 Gm. dose of this acid would require 80 to 120 Gm., 3 to 4 ounces, of dry gelatin, which is more than it is practical to take (A.M.A. Com. Foods, 1936). The widely advertised claim that it prevents fatigue and increases physical endurance is not supported by adequate evidence. Critical tests show no effect on *muscular work* or fatigue in man (Karpovich and Pestrecov, 1941) or in rats (G. C. Knowlton, 1940). It has been tried as a protective colloid in *gastric ulcer*, but without much success.

Gelatin in saline solutions for intravenous injection increases the viscosity of the blood (Burton, Opitz, 1906; Omunt, 1912), prolongs the sojourn in the circulation through its colloidal properties, but leaves the blood fairly rapidly. It was tried and abandoned because of toxic reactions. These may be avoided by using specially selected preparations. It does not sensitize. It is injected as 6 per cent solution (U. S. National Research Council Report, 1944; J.A.M.A. *125*, 284).

Subcutaneous injections of gelatin have been given to increase the *coagulability of the blood*, especially in aneurysm. They are probably ineffective and have the serious objections of severe pain and danger of infection, since ordinary gelatin solutions are often not sterile, and may carry tetanus. Oral administration of 45 Gm. of gelatin daily for two weeks does not change the coagulation time of the blood (Tainter *et al.*, 1939).

Dastre and Floresco, 1897, and Grau, 1910, described increased coagulability of the blood, lasting for several days. The gelatin was injected subcutaneously (100 to 200 cc. of sterile 1 to 5 per cent solution, injected slowly into the thigh, *not* near the aneurysm, every ten to fifteen days, until ten to twenty injections have been given). F. Wood (1902) claimed that the gelatin is just as effective, only somewhat slower, when given by mouth, and recommended eating 3 or 4 ounces of flavored 10 per cent jelly, three times a day.

Pharmaceutical Uses.—Gelatin is employed as an emulsifying agent, as a coating for pills, for making gelatin capsules, and in the form of glycerinated gelatin as a base for pastilles and for suppositories.

Gelatin, U.S.P., is the purified, air-dried product obtained by the partial hydrolysis of the collagen of animal tissues, as skin, ligaments and bones, by treatment with boiling water. Insol. in cold water, but swells and softens when immersed in it, gradually absorbing from five to ten times its own weight of water; sol. in hot water, acetic acid or glycerin; insol. in alc. Watery solutions of 2 per cent or over solidify on cooling. Precipitated by phenol or tannin; not by dilute solutions of metallic salts. *Glycerinated Gelatin*, U.S.P., is made by dissolving water-saturated gelatin in its own weight of glycerin.

Histadine, glutathione, cystine and allantoin are discussed in other sections (see Index).

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CARBOHYDRATE FOODS

These are used therapeutically for rectal and parenteral alimentation (dextrose); for modifying infant food (lactose, maltose and dextrin); in forced alimentation (lactose); and in the diet therapy of diabetes. Starch is considered under Demulcents (see Index).

Dextrose is the form in which carbohydrate circulates in the blood, and is therefore directly available. As it does not require digestion, it may be administered by rectum or hypodermically or intravenously; the last is preferred, especially in fevers, such as pneumonia. It serves also for the introduction of fluid, to restore the blood volume and to increase heat loss in fever. These uses are discussed with Saline Infusion (see Index). Intramuscular injection of 10 per cent solution may be employed in infants.

Dextrose Tolerance in Man.—Normally about 100 Gm. can be ingested before sugar appears in the urine; but as the rate of absorption is limited, the maximum blood sugar level is generally reached with 30 to 50 Gm.; larger quantities only prolong this level. With intravenous injection, glycosuria normally begins when the injection rate exceeds 0.8 to 0.9 Gm. per Kg. per hour (600 cc. of 10 per cent dextrose for 70 Kg.). This is about twice the caloric requirement. *The normal assimilation limits of various carbohydrates* were reviewed by Macleod, 1913 and 1914.

The glycogen content of the liver may be raised to 20 or 35 per cent. Its deposition appears first and is most abundant in the cells adjacent to the central vein of the lobules, and occurs last at the periphery; its withdrawal generally follows the reverse direction (Mann, 1936). The formation of glycogen from its precursor hexose phosphate probably requires alkaline phosphatase (review, Dempsey and Wislocki, 1946).

Intestinal Absorption of Various Sugars.—The concentration of dextrose and galactose solutions does not affect the rate of their absorption from intestinal loops of anesthetized rabbits, thereby implying an active process; while mannose, sorbose and xylose are absorbed proportional to their concentration, indicating passive diffusion. Fructose is intermediate (Verzár, 1935). The intestinal absorption of dextrose is accelerated by the addition of NaCl, if this does not exceed 1 per cent (Glatzel, 1938). The absorption of dextrose from the intestines appears to involve its *phosphorylation*, and is therefore inhibited by phlorhizin and by monoiodoacetate (Gellhorn and Northup, 1934). This is controlled by the adrenal cortical hormone (Verzár *et al.*, 1938).

Absorption of Dextrose from Rectal Injections.—Some of the dextrose is destroyed in the large intestine by bacterial fermentation (E. L. Scott and Zweighaft, 1932), but much is absorbed, sometimes 90 per cent in man, so that the blood sugar level rises by 16 to 25 per cent (Collens and Boas, 1933). In cats' large intestine, the maximal absorption occurs from 6 to 7 per cent solution. A small amount of dextrose is also excreted into the large intestine if it is injected by vein (Büdinger, 1935).

Intravenous Injection of Dextrose on Gastro-Intestinal Motility.—No effects are noted ordinarily if isotonic solutions are used. Hypertonic solutions may augment intestinal propulsion, similar to hypertonic sodium chloride injection (J. P. Quigley and Highstone, 1934). Gastric hunger contractions are not affected even by hypertonic injections (Quigley and Hallaran, 1932; Mulinos, 1933). The addition of 0.1 per cent of dextrose to a bath of Tyrode solution restores the contractions of exhausted excised intestines; d-mannose also produces marked functional improvement; galactose and d-fructose are ineffective, although the galactose is metabolized as well as the mannose (Neukirch and Rona, 1912). Dextrose is indispensable for the contractions of the *perfused mammalian heart*, although this uses less than 0.3 mg. per Gm. of muscle per hour (Cruikshank, review, 1936). Sucrose can not take its place. Increase of dextrose above 0.1 per cent does not cause further improvement (except osmotically), nor does it do so if insulin is added (Geiger and Hambourger, 1938).

***Dextrose, U.S.P.** (Dextrosum; *d*-Glucose), is a sugar ($C_6H_{12}O_6 \cdot H_2O$) usually obtained by the hydrolysis of starch; a white, crystalline or granular powder, odorless and sweet; very sol. in water (1:1), sol. in alc. (1:60). As a nutrient, by mouth, to 180 Gm., 6 ounces daily. Intravenously, 250 to 300 cc. of a 5 per cent (isotonic) to 10 per cent solution, two or three times daily; by enema, 5 to 12 per cent solution. The official dextrose contains 8 to 10 per cent of water. The concentration of solutions must be stated as percentage of this hydrated dextrose. (See Index for *Dextrose Injection* and for Dextrose and Sodium Chloride Injection.) *Liquid Glucose*, U.S.P., is *not* dextrose, but a product of the incomplete hydrolysis of starch, chiefly dextrose, maltose, dextrins, and water; a colorless or pale yellow, sweet, syrupy liquid. Water sol., sparingly sol. in alc. Used as a food.

Levulose is now available at reasonable cost. It is sweeter than saccharose. It has been used in diabetes, but aside from its greater sweetness, its value is questionable. It is readily oxidized in the body, but probably by a different route than is dextrose. A part is converted into dextrose; this involves both the liver and the gastro-intestinal tract (F. C. Mann and Bollmann, 1930). It is deposited as glycogen in pancreatic diabetes, when dextrose is not (E. Neubauer, 1909). *Levulose* (Laevulosum; Fructose) is a white or cream-colored hygroscopic, crystalline powder; prepared from invert sugar or from honey; odorless, a very sweet sugar.

Sucrose, U.S.P. (Saccharose, Saccharum, Cane-Sugar or Beet-Sugar), is inverted in the intestines before it is absorbed or utilized. This occurs so rapidly that the blood dextrose of diabetic patients is increased in a few minutes after its oral ingestion (J. M. Rabinowitch, 1946). On direct intravenous injection, less than a third is inverted and used, practically none in man. The remainder is excreted in the urine, and a small fraction in the feces (Mendel and Mitchell, 1905; Mendel and Kleiner, 1910; N. M. Keith *et al.*, 1933; Power and Keith, 1936; Heilner, 1911; Kuriyama, 1917).

Lactose is a disaccharide which is isolated from milk. Like sucrose, it is not available directly, or on intravenous injection, but must be inverted in the intestines into dextrose and galactose. Since it is less sweet than sucrose, it is used chiefly in infant feeding, and in pharmacy as a diluent for powders and tablets.

Lactose is also a fairly efficient osmotic *laxative* (9 to 15 Gm., 2 to 4 drachms, in warm milk, an hour before breakfast) and *diuretic* (100 to 200 Gm. per day). On *intravenous injection*, lactose is excreted rapidly by the urine if the kidneys are normal (O. Schwartz and Pulay, 1915). Rats, young or adult, fed with large quantities of lactose (50 to 70 per cent of the diet) or galactose or xylose (25 to 35 per cent) develop mature *cataract* within four weeks (H. S. Mitchell and Dodge, 1935; Borley and Tainter, 1938; Darby and Day, 1939). Cataract changes develop in the rat embryo when galactose is fed to the mother (Bannon *et al.*, 1945). Glucose does not have this effect, nor does daily hypodermic injection of galactose (Selle, 1940). Massive doses of thiamine chloride and of riboflavin are not protective (H. S. Mitchell and Cook, 1938). Three groups of experimental cataract may be differentiated in rats (W. Buschke, 1943): (1) *Dystrophic:* tryptophane deficiency, riboflavin deficiency, thallium poisoning. (2) *Tetanic:* dietary and postoperative. (3) *Dietetic:* galactose, xylose, experimental diabetes. Human cataracts may permit the same grouping. The galactose cataract of rats is retarded or even prevented by adding about 40 per cent of wheat-germ to the diet (R. Lecoq, 1943).

An isomer, *beta lactose* (obtained by crystallization above 93° C.) is sweeter and more soluble than the official alpha lactose. It also provides a better medium for B. acidophilus and is therefore more effective for increasing the acidity of the intestinal contents (C. S. Robinson and Gilliand, 1937).

***Lactose,** U.S.P. (Saccharum Lactis, Milk Sugar) $C_{12}H_{22}O_{11} \cdot H_2O$, occurs as white, hard crystalline masses or powder, odorless, faintly sweet taste. Sol. in water (1:5), almost insol. in alc.

Galactose is used for testing hepatic function, since it is metabolized exclusively by the liver, independently of insulin (Shay *et al.*, 1931).

Mannitol (Mannite) and **Dulcitol** are unfermentable sugar-alcohols which occur in different varieties of *manna*, an exudation from an oriental species of ash. They are but slightly metabolized or deposited as glycogen on introduction into the blood, and do not relieve insulin shock, nor do they cause glycosuria in diabetes. Their primary anhydrides (mannitan and dulcitan) and secondary anhydrides (mannide and isomannide) are still less utilizable (M. Jaffe, 1883; Carr *et al.*, 1933; Krantz *et al.*, 1935; Dozois *et al.*, 1935). Mannitol is used intravenously to measure glomerular filtration, as it is neither excreted nor reabsorbed in the tubules. It has been proposed as a sweetening agent in diabetes, but its taste is not very sweet. Doses of 20 to 30 Gm. (5 to 8 drachms) are laxative.

Inositol, inosite, hexahydroxybenzene, $C_6H_6(OH)_6$, has the empirical formula of sugars, but its structure is entirely different. It occurs in animals as "muscle sugar." *Phytin*, a substance present in the seeds, roots and tubers of numerous plants, consists of inosite conjugated with phosphoric acid, presumably as inosite hexaphosphoric acid combined with calcium and magnesium.

Inositol is a food factor or vitamin ("Bios I," E. V. Eastcott, 1928) essential for mice and rats. In these animals its deficiency causes alopecia, deficient growth and other symptoms (Woolley, 1940, 1942; Pavcek and Baum, 1941; Cunha, Kirkwood *et al.*, 1943). It is a **lipotropic agent** (see Index), synergistic with choline, affecting the neutral fat more than the cholesterol (Forbes, 1943). Kultz, 1874, found on feeding inosite that only insignificant amounts appear in the urine, and that diabetic glycosuria is not increased. From this he thought it might serve as a sugar substitute in diabetes. It soon appeared, however, that it is not burned (R. J. Anderson, 1916), the greater part being eliminated unchanged by the feces. Greenwald and Weiss, 1917, claim that it is slowly but completely converted into sugar in phlorhizin-diabetic animals. In man, daily doses of 0.5 Gm. per Kg. cause diarrhea (J.A.M.A., *67*:900, 1916).

Foods for diabetics are intended to reduce the intake of sugar-forming carbohydrates. They fall into two groups: sugars and carbohydrates that do not yield dextrose; and flours for diabetics. None are really satisfactory, and they are little used in the modern treatment of diabetes. Levulose and lactose are sometimes better tolerated than other sugars (v. Noorden, 1910; Goudberg, 1913), but the difference is not important. Grafe, 1914, reported promising results with *caramelized sugar*, which is well absorbed and completely tolerated even in severe diabetes. It does not increase the blood sugar, and the respiratory quotient indicates that it is utilized in the diabetic as well as in the normal organism, but its use has not been extended.—*Flour for diabetics* is intended to form a substitute for bread, as a vehicle for butter, and so forth. High food value is not desirable. *Gluten flours* should not contain more than 10 per cent of carbohydrates. Other flours consist of soy-bean meal or casein.

Inulin, a sweetish polysaccharide occurring in the tubers of "Jerusalem artichoke," dahlia and other plants, was introduced as a nondiabetic carbohydrate, but H. B. Lewis and Frankel, 1914, found it quite useless. It is not digested, although some is burned by the intestinal bacteria. None is converted into utilizable carbohydrate, even in phlorhizin animals. Intravenous injection of inulin is used as a test of renal function. When it is not properly purified it produces febrile reactions (H. W. Smith *et al.*, 1938). Intravenously injected insulin is excreted exclusively through the glomeruli and is used as renal function test. It is harmless if it is pure, but impure products may cause a severe colloidoclastic reaction (W. C. Hueper, 1945).

INSULIN

Insulin is a definite crystallizable substance (a protein of high sulfur content) formed exclusively in the Langerhans islets of the pancreas, essential for the normal metabolism of sugar. It is used in the treatment of diabetes mellitus.

Source of Insulin.—Insulin appears to be formed solely in the "beta" cells of the islets of Langerhans, its output being adjusted in an unknown manner to the blood-dextrose level. It is not stored in any other organ (reviews of Best, 1935; Macleod, 1934). *The insulin content of the pancreas* is quite similar in different species, generally of the order of 1 to 4 units per gram of pancreas. It varies in individuals, especially with age and diet. It is lowered in experimental diabetes by extensive partial excision of the pancreas, by alloxan, and by injection of anterior pituitary extracts. It may also be decreased by conditions which diminish the need for insulin, such as injection of large doses of insulin in rats, by fasting, and by feeding fat. It may be increased by administering estrogens, thyroxin, and certain anterior pituitary extracts. High income of carbohydrates does not raise it above normal. The regulation of its level is complex and little known. Anesthesia by barbiturates does not alter it materially (review, R. E. Haist, 1944). The yield per kilogram of normal human pancreas is 216 to 263 units; reduced in diabetes to 50 to 130 units (Pollak, 1926).

Historical.—Prompted by the dependence of diabetes on injury of the islands of Langerhans, many investigators sought for a sugar-metabolizing hormone in the pancreas. Some rather suggestive but inconclusive data were obtained, for instance by Zuelzer and by Murlin. It may now be seen that the failures of the older workers are to be attributed to the want of sufficiently delicate methods of blood analysis to give definite indications of successful results; to partial destruction of the hormone by tryptic digestion in the course of isolation; and to the high toxicity and local irritation of the insufficiently purified extracts, which complicated and obscured the antidiabetic effects.

F. G. Banting, 1920, conceived the thought of avoiding the tryptic digestion by destroying the ferment-secreting cells by previous ligation of the pancreatic duct. Under the direction of J. J. R. Macleod, and with the aid of Best (Banting and Best, 1922), he put this to trial, and succeeded in demonstrating that the extract of the ligated pancreas lowered the blood sugar level of depancreatized dogs. The practical preparation of the purified insulin from ordinary pancreas was then worked out by Collip, 1923; and the large scale production by the firm of Eli Lilly and Company.

The preparation of insulin requires the prompt arrest of proteolysis, and separation from irritant and toxic proteins. This is secured through the method of Collip, 1923, by extraction of the fresh pancreas of cattle, with cold acid alcohol, and purification of the filtrate by precipitation at the isoelectric point. The precipitate is dissolved in slightly acidulated water (*p*H 2.5), filtered through Berkefeld filters, and standardized by bio-assay. This solution constitutes the "ordinary" insulin. It may also be prepared by other methods; for instance, adsorption on freshly precipitated benzoic acid (Maloney and Findley, 1923).

Chemical Properties.—Insulin is a true and typical levorotatory protein. It is freely soluble in water, except between *p*H 5 and 6. It is also soluble in alcohol, except at the isoelectric point. It is precipitated by half saturation with ammonium sulfate. It is not demonstrably dialyzable. It is readily adsorbed on charcoal, etc. (E. A. Doisy *et al.*, 1923), and its potency is greatly reduced by passing through a Berkefeld filter (Bert and Macleod, 1923). It is not injured by moderate heating with decinormal acid, but dilute alkalis destroy it at blood heat, though rather slowly (Dudley, 1923). Commercial insulin stored at room temperature loses 20 per cent of potency in a year, 25 to 30 per cent in two years (R. L. Grant, 1946). Its activity is completely destroyed by the proteolytic ferments, pepsin, trypsin and papain (E. J. Witzemann and Lioshis, 1923). Its action is apparently connected with a peculiar linkage of its amino acids, involving among others the dithio (-S-S-) linkage (review, Geiling, Jensen and Farrar, 1937). It is an active antigen, but without species specificity (J. H. Lewis, 1937; C. Bernstein *et al.*, 1938).

Crystallized insulin was first prepared by Abel, 1926. It occurs as minute crystals and is levorotatory. It is a typical protein, with a rather high sulfur content (3.2 per cent, exclusively in disulfide linkage), and a high molecular weight, estimated between 20,000 and 50,000. The activity is uniformly about 24 units per mg., regardless of the source; it is destroyed by hydrolysis; none of the fractions are active in any degree (Jensen and Evans, 1934).

Crystalline Zinc Insulin.—Attempts to crystallize insulin by Abel's method often gave unsatisfactory yields, till D. A. Scott of Toronto found that the addition of traces of zinc chloride to buffered solutions of insulin results in ready crystallization and high yields. It is probable that the insulin exists in the pancreas as a zinc compound, for the pancreas normally contains relatively considerable zinc (Lutz) and cobalt and nickel (Bertrand), and the zinc content falls in diabetes even more than the insulin content (Scott and Fisher, 1938). Zn, Co, Ni and Cd all facilitate crystallization, but zinc is the most satisfactory. Crystalline zinc insulin is perhaps somewhat more slowly absorbed than the ordinary insulin, and its action therefore slightly more lasting, but the difference is not significant (Marble and Vartiainen, 1939; Ricketts and Wilder, 1939).

Protamine Zinc Insulin.—Hagedorn *et al.*, 1936, found that suspensions of the precipitate which is formed by adding a solution of protamine (spermine) to insulin, are absorbed from hypodermic injections much more slowly than insulin solution and therefore give better utilization and more prolonged action. D. A. Scott and Fisher, 1936, found that this occurs only if the solution contains zinc (or the related metals), and therefore insure this by the addition of zinc chloride to the solution (A. M. Fisher and Scott, 1937). A great variety of analogous compounds are easily prepared, but it is undesirable to multiply therapeutic forms unless they have definite advantages. *Globin insulin* ranks in speed of absorption between plain insulin and protamin insulin. Tannic acid precipitation of insulin also prolongs the action (F. Bischoff, 1936).

Standardization.—Insulin solutions are standardized in "units" by comparing their ability to lower the blood sugar level of rabbits with a reference standard sample of U.S.P. Zinc Insulin Crystals. The official directions must be followed. The production of convulsions in mice is also used for experimental work. It likewise requires comparison with the reference sample. The *unit* is equivalent to 0.125 mg. of the standard powder, or about 0.04 mg. of crystallized insulin (the application of statistical methods is described by C. I. Bliss and Marks, 1939).

Phenomena of Insulin Deficiency.—Insulin is an important factor in the endocrine balance that determines the normal blood sugar level. It is necessary for the first and final stages of the normal metabolism of sugar, for the deposition of glycogen, and for the oxidation of the dextrose. Deficiency of insulin, resulting from excision of the pancreas or from degeneration of the islands of Langerhans as in diabetes mellitus, results in rise of the blood sugar from the normal level of 0.08 to 0.12 per cent (of the whole blood) to 0.2 per cent in moderate and 0.3 per cent in severe diabetes, with temporary values up to 1 per cent or higher when sugar or other glycogenic substances are ingested. In pancreatectomy, these levels may be reached within twenty-four hours. When the level exceeds the "renal threshold," which varies between 0.1 to 0.23 per cent, but is generally about 0.15 per cent to 0.18 per cent, dextrose may be demonstrated by the ordinary qualitative tests in the urine (glycosuria). The volume of the urine and the consumption of water are greatly increased. Other phases of metabolism are also deranged, chiefly secondarily. Overproduction as well as deficient utilization of sugar are probably both concerned in the hyperglycemia. The nitrogen excretion is increased, the phosphate excretion diminished. The glycerol of fats may be converted into glucose. The combustion of fats is incomplete, resulting in mobilization of fat deposits, lipemia (also increase of phospholipids and cholesterol esters), ketosis and acidosis, which culminate in diabetic coma. Before this, the subject becomes emaciated, with a marked decrease of resistance to surgical operations, gangrene, infections and any other heavy demands. Dogs die within two weeks after excision unless insulin is administered (Best, 1935).

Actions of Insulin.—The best established effects of insulin are: (1) withdrawal of sugar from the blood and its deposition as glycogen in the muscles; (2) decrease of hepatic glycogenolysis; (3) decrease of hepatic gluconeogenesis from noncarbohydrate precursors. The immediate cause of the diabetic hyperglycemia is failure to regulate the blood sugar level. There is no absolute decrease in the rate of sugar utilization by the tissues at large, but the liver fails to respond normally to the inhibitory stimulus of hyperglycemia. Instead, it wastes the protein and fat of the body to pour unneeded sugar into the blood (review, S. Soskin, 1941).

The mechanism of action of insulin appears to consist in abolishing the inhibitory effect of an anterior pituitary hormone on the hexokinase which phosphorylates glucose into the form in which it is metabolized, glucose-6-phosphate, by the aid of adenosine triphosphate (W. H. Price, Cori and Colowick, 1945). Excess of insulin produces too rapid phosphorylation, with fall of blood sugar and accelerated glucose metabolism. Excess of the anterior pituitary hormone has the opposite effects Several questions, however, remain to be cleared up (review, D. Stetten, 1946).

The *normal blood sugar level* is similar in the different mammals, the mean ranging between 0.07 per cent in sheep to 0.12 per cent in rabbits. It is much higher in birds (0.21 per cent), and these are much more resistant to insulin than are mammals, and the latter much more than cold-blooded animals (Macleod, 1934). A carbohydrate meal may raise the level in normal man by 0.2 per cent; glucose may raise it above 0.15 to 0.16 per cent (V. C. Myers, 1924). The sugar exists in the plasma practically entirely as ordinary fermentable dextrose. The 10 to 30 mg. per 100 cc. of reducing substance that is not fermented by yeast (Hiller *et al.*, 1925) consists chiefly of glutathione (R. S. Benedict and Newton, 1929). The corpuscles contain a fairly constant concentration of dextrose over a considerable range of plasma concentration; but the plasma concentration is always the higher (M. H. Power and Greene, 1931).

Ketosis.—The disturbance of fat metabolism is indicated by the increase of ketone substances, beta-oxybutyric acid, aceto-acetic acid and acetone, in the blood and urine. These are probably not abnormal products of the incomplete combustion of fats, as was formerly thought, but normal intermediates in the conversion of fat into sugar, and therefore produced in excessive amounts when the formation of sugar from fat is large (review, S. Soskin, 1941). They lead to loss of fixed base and so to acidosis. Their effects may be so severe that animals die of coma before the fat depots are depleted. The coma is perhaps due partly to acidosis, partly to the special toxicity of aceto-acetic acid, which causes air hunger or depression of the respiratory center. It is decomposed in the body into acetone and CO_2. Beta-oxybutyric acid is relatively nontoxic (Best, 1935).

Ketosis may also result from other conditions that accelerate oxidation of fat to compensate for deficiency of glycogen; by hypersecretion of thyroid or pituitary; by hepatitis, infections, surgical procedures, vomiting, etc. (I. A. Mirsky, 1942).

Oxidation of pyruvic acid by brain dispersions is increased by insulin (Banga, Ochoa and Peters, 1939), but this is not very striking (W. C. Stadie, 1943). Insulin administration to depancreatized dogs increases the formation of pyruvic acid after administration of dextrose (Bueding, Fazekas *et al.*, 1943). K. O. Kaplan and Greenberg suggest that the increase of adenosine triphosphate of the liver by insulin administration indicates that the action of insulin consists in augmented oxidation of pyruvic acid. Insulin increases the consumption of oxygen by slices of liver, if succinate, pyruvate or citrate are present (Corley and Somers, 1946). It appears necessary for the phosphorylation and utilization of *thiamine* (Foa *et al.*, 1946).

Effects of Insulin Administration.—The injection of insulin increases the combustion of sugar and at the same time increases the deposition of glycogen. Both actions combine to lower the level of the blood sugar, and therefore suppress all glycosurias that are due to hyperglycemia, such as pancreatic, puncture, epinephrine, asphyxia, carbon monoxide, ether, morphine, iodo-acetate (Irving, 1934). Phlorhizin glycosuria is diminished.

Appropriate doses of insulin relieve all the phenomena of diabetes mellitus and pancreas excision. They restore the ability to metabolize sugars and fats in the normal manner; they prevent excessive breakdown of proteins; the ketosis disappears rapidly; glycogen accumulates in the liver in normal amounts; the muscle glycogen may be increased; the respiratory quotient rises. Adult depancreatized animals survive for years if insulin is administered with a suitable diet (including raw pancreas to furnish lipocaic or choline).

The fate of the blood sugar that disappears after the insulin is not identical in diabetic and in normal animals. In diabetic animals the sugar is fully accounted for by the increased sugar combustion (increased oxygen consumption and rise of respiratory quotient) and by the storage of glycogen in the liver, and sometimes in the muscles. These changes are also produced in normal animals, and are considered an adequate explanation by Dale, and by Cori and Cori. Increased glycogen deposition by insulin occurs only if the blood sugar level is high (J. J. R. Macleod, 1934). It is more marked in depancreatized animals because their liver is poor in glycogen, while that of normal animals is already optimal. The muscle glycogen is not mobilized by insulin, even after pancreatectomy or epinephrine (review, S. Soskin, 1941). Insulin is not essential to the deposition of liver glycogen (Cori and Cori, 1929).

The *addition of insulin to shed blood* does not accelerate its glycolysis, but if the blood is perfused through an excised heart, the insulin hastens the disappearance of its sugars (Burn and Dale), although this does not appear to be oxidized, for there is no proportionate increase of oxygen consumption or rise of respiratory quotient. Similarly, after large injections of dextrose into normal animals, only some 70 per cent can be satisfactorily accounted for (Kay and Robison). Addition of insulin *in vitro* to minced pigeon muscle maintains a better oxygen consumption (Krebs and Eggleston); but this effect is not seen with mammalian or chicken muscle, and therefore is not of general significance (Shorr and Barker, 1939).

Primary Hyperglycemia.—Intravenous injection of ordinary insulin solutions may cause a temporary rise of the blood sugar level, apparently by direct mobilization of liver glycogen (M. Burger and Kramer, 1929), but this is due to an impurity, for it is not produced by pure crystalline insulin (E. M. K. Geiling and De Lawder, 1930).

Inorganic Serum Phosphate.—The insulin fall of blood sugar is accompanied by a simultaneous fall of the potassium and phosphate concentration of the blood (Harrop and Benedict, 1924), while the calcium concentration rises (Hausler and Heesch, 1925). The phosphate fall may be followed by a rise, often higher than the control level (R. Ellsworth and Weinstein, 1933). Tracer experiments with radioactive phosphate show that insulin facilitates the transfer of inorganic phosphate from the blood to the tissues, especially to the liver, and promotes the phosphorylation of dextrose (Kaplan and Greenberg, 1944). Removal of the pancreas raises the phosphate level, and this is not promptly lowered by the administration of sugar or by epinephrine, as in normal animals. *The amino acid level of the blood* is lowered by insulin, and also by epinephrine in normal rabbits. Insulin becomes ineffective after excision of the adrenals (while epinephrine continues effective). This insulin action is, therefore, due to stimulation of the secretion of epinephrine (B. L. Davis and Winkle, 1934). *The uric acid excretion* is increased by insulin, in rabbits, through the mobilization of epinephrine in response to the low blood sugar level (S. P. Miller and Kuyper, 1938).

Endocrine Antagonists of Insulin.—*Epinephrine* and *thyroxin* antagonize insulin by mobilizing liver glycogen; but with thyroxin this is more or less offset by the increase of basal metabolism. Hypodermic injection of *posterior pituitary extract* raises the blood sugar and inhibits insulin convulsions (Burn, 1923); but this does not occur with intravenous injection. It is therefore attributed to decreased absorption by vasoconstriction (M. Griffiths, 1941). The *anterior pituitary* is the most important antagonist, so that its removal allows depancreatized animals to live over a year without insulin, with very mild symptoms of diabetes, which become severe when anterior pituitary extract is injected (Houssay; review, E. M. Geiling *et al.*, 1937). *Excision of liver* does not prevent insulin hypoglycemia, but hinders the subsequent restoration of the blood sugar level (F. C. Mann and Magath, 1923). Removal of the *suprarenal cortex* results in hypoglycemia in some animals. A diabetogenic factor is found in aqueous extracts of *crustacean eyestalks*, probably formed in the sinus gland of Hanstrom (Abramowitz *et al.*, 1944).

Injection of insulin into chicken eggs before incubation results in lack of caudal vertebrae (rumplessness). The action appears to require the intact insulin molecule (Landauer and Lang, 1946).

Other Interrelations.—*Phlorhizin* does not modify the depressant action of insulin on the blood sugar; insulin therefore diminishes the glycosuria, though it may not suppress it entirely. The indirect effects on the nitrogen excretion have not been sufficiently cleared up (F. P. Nash, 1923; M. Ringer, 1923; C. T. Cori, 1923). *In vitamin B_1 deficient pigeons*, insulin administration restores the ability to store glycogen, and therefore improves the assimilation of the polished rice; but it does not remove the polyneuritis (Bickel and Collazo, 1923). *Cysteine*, administered hypodermically, diminishes the hypoglycemic action of insulin (H. R. Jacobs, 1938). *Cooling* rabbits below 30° C. prolongs the hypoglycemic action of small doses, and the survival after large doses (D. B. Tyler, 1939).

Anesthetics decrease the response to insulin; chloralose and amytal relatively little (review, Geiling *et al.*, 1937). *Acidosis* decreases and alkalosis increases insulin efficiency. Severe diabetic acidosis therefore requires larger doses (Battie and McDowall, 1927).

Alloxan Diabetes.—Intravenous injection of alloxan, 50 to 75 mg. per Kg. for dogs (Goldner and Gomori, 1943); 200 to 400 mg. per Kg. for rabbits (Dunn *et al.*, 1943), rats (Shaw and McLetchie, 1943), and monkeys (Banerjee, 1944), produces almost complete coagulative *necrosis of the beta cells of the islands* of Langerhans within twenty-four hours, without change of the alpha cells or acinar tissue (E. Duffy, 1945). Larger doses cause fatty changes in the liver and necrosis of the renal tubules. The blood sugar goes through three stages: (1) a temporary rise, attributed to direct action on the liver; (2) transitory hypoglycemia probably by lack of dextrose production in the liver, occurring also in pancreatectomized animals (Houssay, Orias and Sara, 1945); (3) hyperglycemia, due to the destruction of the Langerhans cells, persisting indefinitely (rabbits survive up to nine months; Duffy, 1945) and closely resembling clinical diabetes (Dunn, Sheehan and McLetchie, 1943). Insulin, if administered, is not inhibited by alloxan. *Alloxantin* is similarly diabetogenic (Koref *et al.*, 1944); also *styryl-quinoline*. Many closely related compounds are not (Goldner and Gomori, 1944); nor is uric acid, violuric acid, etc. (Thorogood, 1944).

The susceptibility of rats to alloxan is increased by thyroid administration, decreased by thyroidectomy (Houssay and Sara, 1945; C. Martinez, 1945). Reports as to diet appear contradictory (Martinez, 1945; J. H. Burn, Lewis and Kelsey, 1944).

Actions of Insulin on the Gastro-Intestinal Tract.—In intact normal animals, injection of insulin tends to increase the activity of the stomach and intestines. It is mildly depressant for isolated intestines.

In normal human subjects, injection of 40 to 50 units of insulin shortens the *emptying time* of the stomach by about ninety minutes (E. Wiechmann and Gatzweiler, 1927). Intravenously it causes immediate depression, followed within twenty minutes by hypermotility and accelerated evacuation (D. Simici *et al.*, 1927). The increased tonus and hunger contractions may usually be inhibited by injecting sugar into the duodenum, or by atropine or epinephrine hypodermically (J. P. Quigley, Johnson, and Solomon, 1929). Clinically, the tonus of hypertonic stomachs is diminished within fifteen minutes after injection of 30 units, in contrast to the increased tonus observed with hypo- and orthotonic stomachs (P. Marcovich and Decleva, 1929). *Gastric secretion* is also stimulated by the hypoglycemia (La Barre, 1931). This effect is chiefly cerebral. It is transmitted by the vagus and abolished by atropine.

With segments of rabbits' small *intestines* in Ringer's solution, insulin produces a brief depression, followed by more lasting stimulation. The depression appears to be due to sympathetic stimulation, for it is prevented by ergotoxine. The augmentation is probably muscular, for it is not inhibited by atropine (Barlow, 1931). However, I. Cavel and Milcou, 1933, claim that atropine antagonizes the stimulation of guinea pig intestine.

Actions of Insulin on the Heart.—Insulin increases the efficiency of the mammalian heart-lung preparation (M. B. Visscher and Miller, 1927). Moderate concentrations also augment the rate, amplitude and tonus of the perfused frog heart, probably by sympathetic stimulation, for electric stimulation of the accelerator nerve does not result in further quickening, and ergotoxine inhibits the action. The response to vagus stimulation and to atropine is not affected. High concentrations of insulin paralyze the cardiac muscle (O. W. Barlow, 1931). The cardioinhibiting center is stimulated when insulin is perfused through the turtle brain (Barlow). In the Starling heart-lung preparation, the addition of insulin increases the output, with tendency toward systole, and diminishes the coronary flow (Bodo, 1928).

Phenomena of Hypoglycemia "Insulin Shock."—If the dosage of insulin is such as to reduce the blood sugar too much below the normal level, depressive and convulsive symptoms develop, both in normal and in diabetic individuals. They can be promptly and completely removed by restoring the normal blood sugar level by the administration of sugar. The hypoglycemic symptoms start with listlessness, weakness and fatigue, tremor, profuse sweating (which is especially significant) of the hands and forehead; then palpitation, hebetude, mydriasis, diplopia, pallor. The respiration and blood pressure are normal, the pulse normal or sometimes rapid. If the course is not checked, it progresses to acute distress, mental disturbances and coma, followed by irregular convulsions, which may last for hours. These may lead to death, but clinical cases infrequently progress so far (Joslin, 1935). Untreated convulsions are fatal in 40 per cent of the animals. Normal rabbits of 2 Kg. require about 3 mg. for convulsions.

Hypoglycemic Level and Symptoms.—The phenomena are proportional to the lowering of the level of the blood sugar; but the critical level varies somewhat for different species, individuals and conditions. They depend on the rate as well as the extent of the fall; they occur at a higher level if the fall is rapid. In man, symptoms begin usually at the blood sugar level of about 0.07 per cent, and coma at about 0.035 per cent (Banting, Campbell and Fletcher, 1923); but these levels are raised if the blood sugar has been persistently high, and if the reduction is abrupt. Rabbits become convulsive between 0.047 and 0.037 per cent; dogs are very resistant, 0.018 per cent, Banting). *Birds* are more resistant than mammals as regards blood sugar and convulsions (K. K. Chen, Anderson and Maze, 1945). Pigeons, which have normally a rather high sugar level (0.15 to 0.185 per cent), do not show any noticeable symptoms at 0.08 per cent, but their ovulation is decreased (O. Riddle, 1923).

Localization of the Hypoglycemic Convulsions.—The type of the asymmetric and irregular convulsions, similar to those of asphyxia, points to the midbrain or medulla. The latter may suffice, for decapitated cats also go into convulsions when the blood sugar falls to 0.045 per cent. (Ohmsted and Taylor, 1926); but the dominant location is probably in the midbrain.

Insulin fatalities in the clinical shock treatment of schizophrenia show diffuse lesions, most marked in the medulla; aseptic meningitis, edema of the cerebral parenchyma, diffuse degenerative changes in the ganglion cells, insignificant reactions of the neuroglia, absence of perivascular infiltrations. The changes in the ganglion cells are reversible and therefore are not the cause of death. Similar but less marked changes are seen in death from metrazol and from barbital, and in poisoning by strychnine, phosphorus, and arsenic (G. B. Hassin, 1939). Ferrac, 1942, describes rarefaction in cortical areas, due to the gradual disappearance of the nerve cells that had undergone degeneration and disintegration as the result of insulin in schizophrenia treatment. In animals, metrazol produced much less damage than insulin (Winkelman and Moore, 1940). The brain of dogs and rabbits shows diffuse and focal histologic changes from the cortex to the medulla, after acute or chronic insulin poisoning, parallel to the dosage and the duration of the intoxication; with degeneration especially in the temporal lobe, and with convulsed rabbits in the Ammon's horn. The vessels are engorged and sometimes hemorrhagic. Similar changes are observed in morphine, lead and cyanide poisoning, and in uremia (A. Stief and Tokay, 1932).

There are reasons for believing that the convulsions are not due to the hypoglycemia directly, but to some secondary process involving *increased intracranial pressure;* for the cisternal pressure rises rapidly during insulin convulsions in normal dogs, while dogs that have been dehydrated by thirst are not convulsed by insulin, even in massive doses, and in these the cisternal pressure does not rise (D. L. Drabkin and Ravdin, 1930). The lactic acid content of the brain is lowered by insulin (W. E. Stone, 1938). The toxicity has been attributed to *methylglyoxal,* which may be formed by the rapid destruction of glucose and produces convulsions similar to those of insulin, on intravenous injection; but this is difficult to reconcile with the rapid recovery by dextrose injection. The *brain potentials* of rabbits show progressive increase of wave activity, which persists after the convulsions and is abolished by dextrose injection (Goodwin *et al.*, 1938).

Composition of Blood Serum.—At the height of the shock reaction, as induced in schizophrenic patients, and in dogs, the potassium is markedly reduced, by an average of 18 per cent, attributed to hyperactivity of the adrenal glands provoked by the hypoglycemia. The sodium is slightly increased. The nonprotein nitrogen is insignificantly decreased, the protein moderately increased (Keys, 1938).

Antagonism with Narcotics.—Insulin convulsions may be suppressed by narcotics, for instance barbiturates, even with very low blood sugar; but this does not prevent the fatality, which is therefore not due to the convulsions (E. L. Jackson, 1931). The cortical narcotics, urethane and chloral and bromides are also effective against the convulsions (I. Ishigami, 1928), but less so than the barbiturates, whose action is predominantly on the midbrain (Holster and Rusch).

Influence of Other Drugs and Conditions on Insulin Convulsions.—Increase of temperature (Voegtlin and Dunn, 1922) and low barometric pressure (Glickman, 1936) are synergistic, probably through anoxemia. Epinephrine arrests the convulsions by raising the blood sugar, if glycogen is available. Large doses of atropine also delay the convulsions by increasing the blood sugar (X. Chakovitch, 1929), but this is followed by synergistic psychic disturbances (Quigley, 1937). Insulin increases the convulsant action of strychnine and picrotoxin, not that of hexetone, barium or phenol (I. Ishigami, 1928).

The cause of death in insulin hypoglycemia appears to be the inability of the brain to accomplish the oxidation of sugar on which its metabolism depends.

The immediate cause of death is failure of respiration, which does not resume after the postconvulsive apnea; but neither the suppression of the convulsions by narcotics nor artificial respiration prolongs life or raises the lethal dose materially. Nor is there any change in the ability of the tissues at large to utilize oxygen, for the systemic arterial and venous bloods present the normal differences (E. L. Jackson, 1941). In the cerebral vessels, however, the oxygen difference between arterial and venous blood is markedly lowered in insulin coma, and this must be due to decreased metabolism of the brain, for there is no significant change in the intracranial blood flow (Ferris *et al.*, 1941). Himwich *et al.*, 1939, found that the oxygen consumption of the brain is reduced to less than half in hypoglycemic convulsions, due to the diminished supply of carbohydrate for its metabolic needs. This was confirmed for man by W. Goldfarb and Wortis, 1940, who found that alcohol cannot be oxidized in place of sugar.

Relief of Hypoglycemia.—This occurs usually in a few minutes after the oral administration of 5 to 20 Gm. of dextrose, or any other form of sugar (candy or orange juice). If the patient is comatose, the dextrose is injected intravenously, as 50 per cent sterile solution; the patient has usually recovered before 10 cc. have entered the vein, but more may be needed in severe cases (Joslin, 1935). It may be repeated if necessary. If sterile dextrose solution is not available, epinephrine may be injected hypodermically (0.3 to 0.6 cc. of 1:1000), always followed by sugar by mouth. Epinephrine is effective only by mobilizing stored glycogen, and is therefore likely to fail in diabetes (R. S. Lyman *et al.*, 1923).

Other sugars than dextrose, d-fructose and mannose are not effective antidotes. Alkalis and sodium lactate have no effect (E. C. Noble and MacLeod, 1923). Glycerol is effective in rats (Voegtlin, Dunn and Thompson, 1925); dihydroxyacetone and lactic acid are also somewhat effective.

Clinical Efficiency of Insulin in Diabetes Mellitus.—The properly dosed and spaced administration of insulin abolishes the glycosuria, and the excessive glycemia diminishes the thirst and polyuria, removes the emaciation, the edema and the mental inertia, controls the acidosis, lowers nonprotein nitrogen and the creatinine of the blood to the normal level, and restores patients from coma (C.B.F. Gibbs and Sutter, 1923). The effects usually last only during the continuance of the insulin administration; although in the relatively lighter cases a partial restoration of the functions of the pancreas seems sometimes to occur, presumably as an indirect result of the improved health of the patient, by the more liberal diet which is possible with insulin administration.

As pointed out by E. P. Joslin, 1935, clinical diabetes is practically never complete: the manufacture of insulin is not abolished but merely diminished to a degree which varies from time to time. It is improved by careful diet, and deteriorates if the diet is extreme in any direction. Insulin, by making possible a better diet, increases the chances of improvement, so that many patients can progressively reduce the insulin dosage and sometimes dispense with it entirely, although the pancreatic lesion proper is not cured.

The administration of insulin must be adjusted so as to secure a continuous supply and must be augmented when the sugar level rises during digestion. The dosage must be adapted to the individual requirements to permit an optimal diet and to avoid the toxic effects of overdosage. Oral administration is practically ineffective because insulin is not readily absorbed from the digestive tract. Intravenous injection acts promptly, but the total effect is only an eighth to a half of the same dosage hypodermically (Sahyun and Blatherwick, 1928; Aubertin and Tringuier, 1932) because the insulin is too rapidly excreted by the urine (Kepinov and Petit-Dutaillis, 1929). It is, therefore, administered hypodermically. Even with this, considerable insulin is lost by excretion, and the action is relatively short, so that it must be injected two or three times a day. Protamine zinc insulin and globin insulin secure slower and more lasting absorption and action. The hypodermic injection of insulin is somewhat irritant (D. J. Bowie and Robinson, 1923) but not sufficiently to constitute a serious objection, and the irritation becomes less noticeable with continued use (M. Sturtevant, 1924). The site of injection should be changed so that not more than one injection is made in the same spot in a month.

The inefficiency of oral and rectal administration is due chiefly to poor absorption, rather than to destruction of insulin in the intestines or liver (D. Campbell and Morgan, 1933). Insulin is not entirely inert by these channels, but its efficiency is uncertain and therefore does not permit the precision of dosage which is indispensable. Various ways have been tried to produce effective absorption from oral administration, but none has given satisfactory results (Geiling *et al.*, 1937). Various substances do increase intestinal absorption somewhat (R. L. Driver and Murlin, 1941; quinine, Hanzlik and Cutting, 1941). It was claimed (Lesch *et al.*) that *saponin* has this effect: but the difference lies within limits of accidental variation.

Absorption from Other Surfaces.—Absorption from the tongue may amount to a third of the hypodermic, but only with small doses and favorable conditions. It is therefore wasteful and uncertain (B. Mendel *et al.*, 1924). The *conjunctiva* gives quite good absorption, about two-thirds as efficient as hypodermic in rabbits, without material irritation (C. D. Christie and Hanzal, 1931). *Spraying or snuffing into the nostrils* is effective but not uniform (S. Horwitz, 1931). Absorption has been observed from the *vagina* and from the scrotal sac (N. F. Fisher, 1923); and from the intact skin (R. H. Major and Delp, 1937), but is not constant. *Peritoneal injection* is practically equal to intravenous in degree and rapidity of response in dogs (Banting *et al.*, 1923), but it is too irritant for clinical use.

Persistence of Action, Fate, Excretion.—The maximal effect of the blood sugar is reached in two to five hours after the hypodermic injection of unmodified insulin, and in twelve to twenty-four hours after protamine zinc insulin. It then declines gradually. The duration of insulin action, in fasting depancreatized dogs, is proportional to the logarithm of the dose; *i. e.*, to double the duration requires ten times as much insulin; so that the rate of its disappearance increases with the dosage (Greely, 1940). With intravenous injection the maximum occurs promptly, and the decline is rapid. Almost the entire amount can be recovered from the urine, but only 25 per cent after hypodermic injection (N. F. Fisher and Noble, 1923). The remainder is presumably destroyed.

The liver and spleen do not participate in the destruction, for the hypoglycemia is of the same degree and duration if the insulin is injected directly into these organs as when it is administered hypodermically. Incubation with blood for four hours at 37° C. does not inactivate insulin (Mark and Lewis, 1943).

Dosage and Spacing of Injection.—The dosage is expressed in "insulin units"; but the amount of carbohydrate which may be metabolized by a unit varies somewhat with conditions, such as exercise, diet, acidosis, infections, the size of the dose, the nature of the preparation and the frequency of administration. The dosage must, therefore, be adjusted to the individual, eventually by trial.

The insulin output of the normal human adult pancreas is probably between 45 to 80 units daily, and this includes a considerable factor of safety. It has been estimated that 48 units would be adequate even if the diet were chiefly carbohydrate, and that 8 units would suffice in starvation. This natural output is better adjusted to the needs of the moment, however (probably by directive action of the dextrose concentration on the islet cells), and is therefore utilized to better advantage than is the case when the insulin is supplied by injection.

Goldner and Clark, 1944, report that two patients with total pancreatectomy were controlled with less than 50 units of insulin daily, with a dextrose intake of 150 to 200 Gm. Many diabetic patients require more than this amount, so that clinical diabetes appears to involve some interference with insulin action. Sometimes even 1000 units are ineffective (Root). Interfering factors are infections (the mechanism is unexplained), acidosis, overactivity of physiologic antagonists, especially anterior pituitary, thyroid, adrenal, and liver.

A continuous supply gives a more complete utilization, and frequent injections are therefore more economically used than widely separated ones. The slowly but continuously absorbed protamine zinc insulin gives about 20 per cent better utilization than unmodified insulin. The histone zinc insulin compound is absorbed slower, globin zinc insulin faster, than the protamine compound (Bailey and Marble, 1942). Intravenous injections of such preparations do not differ significantly from unmodified insulin (Longwell and Ravin, 1936). Crystallized insulin can suffice for every need if it is injected sufficiently often; but in many cases it may be usefully supplemented by the less absorbable forms (Joslin, 1942). With unmodified insulin a unit metabolizes usually between 1 and 2 Gm. of dextrose, sometimes as high as 5 or 6 Gm., but under ordinary clinical conditions it is safer to assume the average equivalent as 1.5 Gm.; so that two-thirds of a unit of insulin would need to be administered for each gram of dextrose excreted in the urine, on a given diet. Patients whose glycosuria can be suppressed by an adequate diet do not require insulin, except when they face emergencies such as infections or surgical operations. Cases of moderate severity require 5 to 60 units daily; 30 is perhaps the average. Many patients do sufficiently well with one daily injection into the loose subcutaneous tissue before breakfast. With more severe cases, a second injection is made before supper, and a third at bedtime if necessary. The effect lasts about eight hours. In infections, it may be injected at six-, four- or even two-hour intervals (review, Joslin, 1935). *Allergic hypersensitiveness* to insulin, with local and systemic reactions, occurs rather rarely, although the insulin molecule itself may act as antigen (J. H. Lewis, 1937). Sometimes it is species specific, and may then be avoided by employing insulin prepared from another species.

Protamine zinc insulin permits a wider spacing of dosage because of its slower and prolonged action (H. C. Hagedorn *et al.*, 1936; A. Sindoni, 1937). This must be remembered in relation to diet and exertions for the next twelve to twenty-four hours. Hypoglycemic reactions are less frequent than with ordinary insulin, but are likely to set in more insidiously, without premonitory symptoms, and a severe attack may be precipitated abruptly, for instance by exercise (Joslin, 1938). It may be injected once a day, an hour before breakfast or supper time or on retiring, beginning with two-thirds of the dosage of unmodified insulin, and supplementing with one or two injections of the latter if necessary. A mixture of one part of protamine insulin with two parts of ordinary insulin has been used (Colwell and Izzo, 1943). Its delayed action makes it unsuited for the treatment of emergencies. It should never be administered by vein.

Globin insulin with zinc is intermediate between the unmodified and protamine forms. It is administered by deep subcutaneous injection, never by vein. Its effect is maximal between eight and sixteen hours after injection. The daily dose is two-thirds to three-fourths that of unmodified insulin.

In diabetic coma, 30 to 60 units of unmodified insulin should be injected, half by vein and half subcutaneously, followed by 20 units subcutaneously at intervals of one-half to three hours, as needed. It is rarely necessary to use more than 150 units in twelve hours, but 800 have been given. It is important to guard against hypoglycemia; the urine should be examined every hour, and if it becomes sugar free, dextrose should be administered. Normal saline solution may be injected hypodermically or intravenously to offset dehydration. Alkali is not needed (review, Joslin, 1935).

Use of insulin in nondiabetic conditions has been suggested to protect the liver against anesthesia and hepatotropic poisons; and in the management of nondiabetic malnutrition. The hypoglycemia is used in the treatment of schizophrenia and has been suggested (but without good foundation) in opiate addiction.

Insulin in Nondiabetic Malnutrition.—In thin persons, for instance those with tuberculosis, 10 units, three times daily, with a liberal diet, often increases the appetite and starts a prompt gain of weight, at first rapid and then flattening as the normal weight is approached. The gain is generally held after insulin administration is stopped. Patients feel stronger and more active. The red count rises and the effects are probably due to increased food consumption and better assimilation, perhaps by the direct effect of insulin or hypoglycemia on gastric motility and secretion. The nitrogen excretion rises parallel to the weight. The basal metabolism is not affected (review, H. Blotner, 1933).

The hypoglycemic "shock" treatment in schizophrenia was introduced by M. Sakel, 1935. A severe degree of hypoglycemia is induced, and when the patients recover from the collapse and convulsions, the sensorium seems to clear, the patients are more accessible, and marked improvement may persist (J. Steinfeld, 1937). The improvement is probably due to the psychic impression, shocking the patient out of a rut (R. L. Osborne, 1940), but the hypoglycemia has been invoked for insulin (S. Soskin, 1939). The results are variable, and fatalities have occurred from the hypoglycemia. The treatment obtained considerable vogue in psychopathic hospitals, but it has been largely displaced by metrazol. Insulin is now generally preferred for schizophrenia; metrazol and electric convulsions for emotional and other depressions, including the manic depressive syndrome (N. D. C. Lewis, 1945). The results vary widely, depending partly on conditions, partly on criteria. The improvement is generally greatest in patients who are amenable to other methods. Gottlieb and Huston, 1943, conclude that their series did not show better permanent results with insulin than with more conservative methods. Brooklyn State Hospital, 1944, reports marked benefits from insulin shock; a larger proportion of patients returned to gainful occupations and a much larger proportion were able to leave the hospital.

Sakel's routine consisted of an initial *dose* of 60 units, increased daily by 10 to 30 units until the shock-dose had been determined, at 70 to 240 units, then similar reduction to the just effective dose, the total treatment lasting at least sixty days, or ninety days for older cases. *Dangers:* The treatment requires deep and fairly prolonged coma and probably often causes mild and sometimes severe pulmonary edema and embolism (Nielsen *et al.*, 1938). Two-thirds of the patients show various cardiac irregularities, sometimes auricular fibrillation and S. A. block (Bellet *et al.*, 1939). Residual nervous symptoms may occur, analogous to those of prolonged asphyxia (Himwich, Frazekas *et al.*, 1938), and similar irreparable anatomical cerebral lesions (A. B. Baker, 1938). Fatalities are reported in the ratio of 73:10,000 for insulin, 23:10,000 for metrazol (J. L. Kinsey, 1941).

Other Antiglycemic Agents.—Patients sometimes report striking results following the use of various substances, especially plants and plant extracts; but carefully controlled observations generally show that the response is uncertain and scarcely exceeds the ordinary variations of the disease (review, Geiling *et al.*, 1937). The most important of the suggested substitutes is a synthetic guanidine derivative, *synthalin* (see Index), introduced by E. Frank of Breslau, as an auxiliary, with the advantage that it can be used orally. It does have a definite action, but is variable and inferior to insulin, and by a quite different mechanism. Effective doses are likely to damage the liver, so that its use has been practically abandoned.

The *glucokinin* of Collip, a supposedly insulin-like principle from various animal tissues and plant sources, has not been confirmed (C. H. Best, Jephcott and Scott, 1932). *Diastase* is reported to lower normal blood sugar (Deichmann and Myers, 1936). *Scoparia dulcis* is reported to contain an antidiabetic principle (M. C. Nath, 1943). *Myrtillin* extracted from *blueberry leaves* was introduced by Allen as a minor adjuvant to insulin, but has been abandoned (J. J. R. Macleod, 1930). Administered by mouth to cats and rabbits, it does not lower the blood sugar, but in fasting animals it produces a marked rise. Large doses cause initial stimulation and subsequent paralysis of the central nervous system. Continued administration results in cachexia, anemia, icterus and death (Dietering, 1938).

Jambul, the fruit of *Syzygium jambulana*, of Eastern Asia, has been used in diabetes mellitus, in doses of 0.3 to 0.5 Gm., but its efficacy is doubtful. Its constituents are discussed by Hart and Heyl, 1917. It contains an essential oil, tannic acid, and probably a glycoside.

PREPARATIONS.—**Insulin Injection**, U.S.P., is "an acidified aqueous solution of the active principle of the pancreas which affects the metabolism of glucose." It is so standardized that each cubic centimeter contains 20, 40, 80 or 100 U.S.P. units, and is marketed in vials of 10 cc. The concentration should be selected so that the injection approximates ¼ to ¾ cc. It is a clear, colorless liquid, contains 0.1 *to* 0.25 per cent of phenol or cresol, and has a *p*H of 2.5 to 3.5. It may be prepared from highly purified amorphous insulin or from **Zinc Insulin Crystals.**—This contains 0.4 to 0.9 per cent of zinc, or 0.2 to 0.4 mg.

per 1000 units, chemically combined with the active principle. Each milligram of the crystals equals 22 units of insulin.

Protamine Zinc-Insulin Injection, U.S.P., is a suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride and protamine, and marketed in 10 cc. vials as a uniform aqueous suspension, each cubic centimeter containing 40 units of insulin and 0.08 to 0.1 mg. of zinc, or 80 units of insulin and 0.16 mg. of zinc, with about 0.4 mg. of protamine buffered with phosphate to *p*H 7.1 to 7.4. Initial dose about two-thirds that of insulin. It should be shaken before injecting.

Globin insulin is insulin modified by the addition of globin (from hemoglobin) and zinc chloride. It is a clear, aqueous solution, of *p*H 3.7, containing 80 units per cubic centimeter. Daily dose, about two-thirds to three-quarters that of insulin.

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PHLORHIZIN

Injection of this glucoside, which occurs in the apple tree, produces *glycosuria* by blocking the tubular reabsorption of dextrose. It also interferes with other tubular processes and lowers the rate of glomerular filtration (reviews, J. A. Shannon, 1939; F. W. McKee and Hawkins, 1945). It has no therapeutic applications.

The amount of glucose in the urine may be high, above 12 per cent. It persists for several hours after a single injection, but may be prolonged indefinitely at its highest degree, by administering 1 Gm. of the glucoside per kilo of body weight, by mouth, three times a day. Larger doses do not increase the glycosuria. The loss of sugar leads to hypoglycemia, which is compensated by mobilization of the liver glycogen, and by formation of dextrose from protein. The nitrogen excretion is therefore greatly increased. In fasting animals it may rise to four or five times above hunger alone (Reilly, Nolan and Lusk). If the action is continued for some days, the ratio of urinary dextrose:nitrogen becomes stabilized between 2.8 and 3.65, with a respiratory quotient about 0.69. The ability to oxidize sugars appears impaired, probably by the hypoglycemia (Stiles and Lusk). If the depletion of hepatic glycogen is kept up, it leads to fatty degeneration of the liver cells. Diuresis occurs (Loewi and Neubauer, 1908), presumably as a result of the glycosuria, but is relatively small. The excretion of the other solid constituents, salts, protein, etc., shows no constant abnormalities. The oxygen consumption of the kidneys is largely increased. The *milk* after phlorhizin contains the normal amount of lactose, and no dextrose. Traces of sugar appear also in the saliva and gastric and pancreatic juice (R. G. Pearce, 1916). The phlorhizin is *excreted* for the most part unchanged (Pietkiewicz) within two days (Prausnitz). The glycosuria outlasts the excretion.

Historical.—Phlorhizin was isolated by Koninck, 1835, from the root bark of apple, pear, cherry and plum trees. Stas, 1839, showed it to be a glucoside decomposed by acid hydrolysis into dextrose and phloretin; and the latter again into phloretinic acid and phloroglucin. Phloretin has a similar but weaker action. The characteristic glycosuria was discovered by Mering, 1886. It has been produced in all vertebrates tried: mammals, birds, frogs and reptiles.

The Glycosuria Is Not Pancreatic.—The symptoms after phlorhizin resemble those of pancreatic diabetes, but their mechanism is in fact totally unrelated. The most striking difference is the absence of hyperglycemia. With phlorhizin, the sugar of the blood is diminished (Mering)· if the kidneys are excised, or the ureters tied, the blood sugar remains normal (Minkowski).

The Action Is Renal.—It is evident from these experiments that the glycosuria is essentially renal. The effect is peripheral, for it occurs after destruction of the medulla and cord, and after section of all renal nerves (Frey). If the phlorhizin is injected into one renal artery, glycosuria occurs in this kidney and not in the other (Zuntz). As the reabsorption of water is not impeded to a corresponding degree, the concentration of dextrose in the urine rises far above that in the blood (Walker and Hudson, 1937). Histologic changes have been described in the renal epithelium. Carmine and methylene blue, which are excreted by the tubules, may suppress the glycosuria. Minkowski suggested that the phlorhizin acts as a glucosidal vehicle, splitting off its sugar in the kidneys, and again taking up sugar from the tissues; but the quantity of sugar excreted when phlorhizin is injected into the renal artery speaks against this view.

Phlorhizin inhibits *phosphorylation* and dephosphorylation *in vitro*, with yeast and with muscle; also the formation of lactic acid from dextrose or glycogen. Lundsgaard attributes the glucosuric action to disturbance of the phosphorylation mechanism in the renal tubules, interfering with the absorption of dextrose. Kalckar, 1937, showed that low concentrations of phlorhizin inhibit the phosphorylation of hexoses by rabbits' kidneys. Anderson and Squires, 1938, reported marked increase of the phosphatase activity of the serum. Phlorhizin inhibits the oxidation of carbohydrates by slices of rat liver (Wetzel and Meadows, 1937), and also the oxidation of alcohol (Leloir and Munoz, 1938).

The glycosuria is suppressed in severe nephritis (H. W. Hoffmann, 1931), and the injection of phlorhizin (*phlorhizin test*, 5 mg. in warm water, hypodermically) (or 10 mg. in 1 cc. of saline intravenously, Krotozyner and Stevens, 1917) has been proposed as a means of diagnosis. The result, however, is not decisive in either sense. *Oral administration* of large doses (to 32 Gm. in divided doses over three days) causes transient glycosuria and significant lowering of the clearance of urea, xylose and creatinine, without lasting toxic effects (W. Goldring, 1934).

Sources of the Sugar.—The stock of carbohydrates in the body disappears first, although some glycogen is persistently retained (Mering), even in fasting (Sansum and Woodyatt, 1915). Phlorhizin does not mobilize the *hepatic glycogen* directly, but only as a result of the hypoglycemia. On the contrary, when the kidneys are excluded, phlorhizin leads to a reaccumulation of hepatic glycogen. Since there is no hyperglycemia, it appears that phlorhizin stimulates directly the synthesis of glycogen. When the kidneys are intact, this action is overcome by the glycosuria (Epstein and Baehr, 1916). With persistent administration, the sugar is derived from the carbohydrates of the food; and if these are excluded, from the proteins. Pavy, Brodie and Siau (1903) showed that the quantity of sugar which is excreted when the abdominal viscera are excised exceeds the quantity of sugar which disappears from the blood, and that which could be obtained from the limited glycogen depots of the muscle. The D ÷ N ratio shows that this is derived chiefly from protein.

Arbutin, a glucoside found in the leaves of Uva Ursi (see Index), is reported to have glycosuric effects similar to phlorhizin. Both are phenol glucosides. The action is possessed by the alcohol glucoside *salicin*, not by the aldehyde glucoside amygdalin (F. Y. Michel, 1937).

FATTY FOODS

Fats are used therapeutically chiefly for their local protective action and will be considered under Emollients. They are not indispensable in nutrition, but are normally useful because of their high caloric value and their easy storage as reserve fat. This intake should not be reduced below the customary limit. If the intake of fats exceeds the digestive and absorptive capacity of the intestines, they act as laxatives and cause digestive disturbance. If fats are incompletely burned, as in diabetes, or with "*ketogenic diets*" (see Index) rich in fats and poor in carbohydrates, they give rise to ketone acids which render the urine acid and antiseptic.

Fats affect the availability of a number of dietary factors by facilitating their absorption or hindering their oxidative destruction; for instance, carotene and vitamin A (review, Burr and Barnes, 1943). On the other hand, rancid fats destroy most of the vitamins, especially A and E (Fitzhugh *et al.*, 1944).

Some edible fats are important *carriers of fat-soluble vitamins* (review, Cowgill, 1945). *Fish liver oils* contain vitamins A and D; *butter* contains A, carotene, variable amounts of D and small but significant quantities of E; *vegetable oils contain carotene;* oils of *seed embryos* are the richest source of E. *Adipose tissue* and the fats prepared from it, lard, suet and oleomargarine, are practically devoid of vitamins, but margarine is often modified by adding vitamin A.

True fats, the glycerides of fatty acids, constitute the *simple lipids. Compound lipids* include phospholipids, in which one of the fatty acid radicals is replaced by phosphoric acid and choline; glycolipids, and amino lipids. *Derived lipids* include the sterols (Bloor).

The *rate of absorption* of the various true fats does not differ greatly; in rats it ranged from 53 to 58 per cent for partially hydrogenated vegetable oils, and for lard and corn oil, to 68 to 71 per cent for fish liver oil and butter oil (Steenbock *et al.*, 1936).

Absorption of fat from the intestines requires that it be miscible or soluble in water, by emulsification and hydrolysis. The *lipase* of the pancreatic juice splits the fats into glycerol and fatty acids. Free fatty acids combine with free alkali to form *soaps*, which are emulsifying agents, and so give the lipase better access to the fat. This mechanism plays a minor part in the absorption itself, for the formation and the action of soap take place only in freely alkaline reaction, and this exists only temporarily when pancreatic juice and bile are discharged into the duodenum. The fine emulsification is effected chiefly by the *bile salts*, acting on the partly hydrolyzed fat. Bile salts can actually dissolve palmitic and stearic acid into diffusible complexes (Verzár and Kúthy, 1929), but the lipase action does not suffice to carry the hydrolysis of the major part of the fat to this stage, and triglyceride fats are only coarsely emulsified by bile. A. C. Frazer, 1946, finds that bile salts emulsify partly hydrolyzed fats much more effectively, reducing the particle size to less than 0.5 microns, as is the case in the chyme. He believes that particles of this size can pass intact through the canaliculi of the brush border into the absorbing cells of the intestinal epithelium, therefore obviating the necessity that all the neutral fat be brought into actual solution, for which there is no direct evidence; there is, however, evidence of the intact absorption of mineral oil particles of this size. Other agents may presumably substitute for bile, for experiments with deuterium containing dietary fats show that about two-thirds are absorbed in the absence of bile (A. Shapiro *et al.*, 1936). Short chain fatty acids, such as butyric, are sufficiently soluble in water to be absorbed as solution, but of the ordinary fats at least two-thirds would usually be absorbed as unhydrolyzed particles. The absorption of phospholipids, lecithin and cephalin also requires their hydrolysis (presumably partial). Difficultly hydrolyzable fatty acid compounds such as cholesterol esters are not absorbed (review, W. R. Bloor, 1939).

Somewhat more than half of the absorbed fat appears as finely emulsified triglyceride fat in the chyle of the lacteals; the remainder is carried by the portal blood. The chyle fat would correspond to the portion absorbed as particulate emulsion and passed as such through the protoplasm of the absorbing epithelium. The fats of the portal vein would represent chiefly the short chain fatty acids that were absorbed as solution (Frazer). The assumption that the intestinal cells absorb only the hydrolyzed fatty acids would require that they resynthesize these into neutral fats before they pass into the chyle. R G. Sinclair, 1929, suggested that this occurs by phosphorylation; but there is no evidence for either of these assumptions, although there is evidence that some phospholipid may be formed in the intestinal epithelium (Frazer).

The further course of the absorbed fats has been traced by the substitution of deuterium. A small part goes into the liver and other parenchymatous cells. A large part, 20 to 40 per cent, is deposited in the *adipose tissue* before it is utilized, but the fatty acids are generally modified before deposition. Stearic acid may be formed from oleic or palmitic acid. Fatty acids with short carbon chains (butyric to caproic) are not deposited even when fed in large quantity, but are rapidly and completely burned (Schoenheimer and Rittenberg, 1938). The fat depots (even exclusive of the liver) have a steady turnover, with a half-life of six to eight days.

The fat of the liver is of two kinds: (1) that which is an essential part of the cell structure of the gland and does not vary under ordinary conditions, and (2) metabolic lipids, consisting of glycerides, phospholipids, and cholesteryl esters, which vary considerably. The glycerides may come directly from food, or from fat depots: from the latter especially when liver function is depressed by poisons, or perhaps because the liver does not use up fat at the normal rate (review, A. C. Frazer, 1940). Storage of fat in the liver probably involves phosphorylation into lecithin.

The *liver fat* consists of 40 to 70 per cent neutral fat, the remainder being chiefly phospholipids. In dogs on a well balanced diet it is fairly constant at 2.5 per cent of the organ weight, but may be increased to 50 per cent by fatty food. The fat changes are slower than those for glycogen, and are generally in the opposite direction. The liver fat tends to increase in starvation and in chloroform or carbon tetrachloride poisoning, by withdrawal of fat from the other depots (McHenry and Patterson, 1944). Alcohol tends to increase the liver deposition of fed fat. The transformation of fat to carbohydrate is doubtful for normal conditions, but carbohydrate is readily transformed to fat (review, Mann, 1936). Deuterium studies show that the increase of liver fat in fasting, and by anterior pituitary administration, is due largely to transport of fat from other depots. The liver fat that accumulates on high carbohydrate: low choline diet is derived largely from sources other than the depots, probably from the carbohydrates and proteins of the diet (H. M. Barrett *et al.*, 1938).

Liver injury, diffuse or focal necrosis or cirrhosis, is produced in rats by the same dietary changes that produce fatty infiltration of the liver. This is aggravated by excess of l-cystine and diminished by choline, especially with dl-methionine (P. György and Goldblatt, 1942).

Accumulation of fat in the liver may be due either to failure to transport fat out of the liver or to the transfer of fat into the liver from other depots. *The accumulation of fat by diet or after pancreatectomy* is due to failure of transport out of the liver, owing to deficiency of phospholipids. It can be corrected by feeding lecithin (Hershey) or its constituent choline (Best; see under choline) This action of choline was designated as *lipotropic* (Best *et al.*, 1935). *Inositol* acts as a lipotropic factor in rats, probably also by intermediation of phospholipids. Alteration of Vitamin B income renders the liver more resistant to choline, but more susceptible to inositol (review, McHenry and Patterson, 1944).

Lipocaic.—Dragstedt *et al.*, 1936, 1940, demonstrated another distinctly lipotropic substance in alcoholic extracts of beef pancreas, and gave it this name. Its oral or hypodermic administration prevents fatty infiltration and degeneration of dogs' liver after pancreatectomy. It is about twenty times more potent than choline. Its chemistry and mechanism are not known. It is not present in the external secretion of the pancreas, is not related to insulin, and has not been found in any other organ. Its administration is reported to have improved psoriasis in some patients, but its status is experimental (report, Council of Pharmacy and Chemistry, J.A.M.A., *115*, 1454).

The *fecal fat* is, under normal conditions, derived chiefly from the secretions of the intestinal tract, and not from unabsorbed food fat or bacteria (A. Krakower, 1934; A. Shapiro *et al.*, 1936, deuterium method).

Hypodermic and intramuscular injection of fats and oils is used for the conveyance of drugs. It was also suggested for parenteral alimentation, but the absorption is so slow that it is practically worthless (Winternitz, 1903; Henderson and Crofutt, 1905), and the unabsorbed fat leads to fibrosis. Iodized oil, for instance, may be demonstrated for months. Olive oil persists as unchanged globules and causes but little irritation. Cod liver oil is partly converted into amorphous insoluble material and provokes complex reactions. Methyl esters of all acid fractions are hydrolyzed (Hass, 1938). Fat introduced in emulsion intravenously is also burned (Murlin and Riche, 1915), but the utilization is limited and severe secondary anemia may follow (Dunham and Brownschwig, 1944).

Fate of Lipids in the Lungs.—Oils that have entered the bronchioles flow readily into the alveoli and are there engulfed by macrophage cells; but these have little or no capacity for digesting the lipid, nor are they apparently injured by it. The phagocytosis begins in less than half an hour, but with liquid paraffin and with cod liver oil very little has been taken up in seven days. The state of emulsification is important. Vegetable oils are largely eliminated without phagocytosis (J. L. H. Patterson, 1938). The more irritating mineral and fish oils produce gradual proliferation of the septal and interstitial cells, without mobilizing the leukocytes. The oil-filled macrophages persist for long periods in the alveolar spaces. Cod liver oil is particularly irritant and may lead to necrosis of the lung tissue (review, O. H. Robertson, 1941). *Linoleic and linolenic acids*, in contrast to all other fatty acids so far investigated, are not synthesized in the body (deuterium studies, Bernhard and Schoenheimer, 1940) and are therefore indispensable dietary constituents (Burr and Burr, 1930); but so little is needed that they are probably not of practical dietary significance (review, Cowgill, 1945), Their deficiency leads to malnutrition and skin lesions in rats. Minute amounts of linoleic acid are effective against this condition (H. M. Evan sand Burr, 1928; Burr, 1929). and it was misnamed "*vitamin F.*" Prolonged administration of excessive amounts of unsaturated fatty acids acuses hemolytic anemia (Yonechi, 1935).

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CHOLESTEROL

Cholesterol is familiar expecially as a constituent of gallstones, but it occurs in all animal cells. It is a difficultly soluble lipid and a chemically inactive monatomic alcohol. Its role in the economy of life has been puzzling. It forms chemical compounds with saponins and therefore protects against hemolysis by these poisons, but this, of course, is not a natural function. The cholesterol content of the blood changes with its other lipids, but this might be a secondary phenomenon. Its administration to rabbits produces arterial lesions, but these are not paralleled in man. Irradiation with ultraviolet light transforms it into viosterol derivatives, and through these it plays a part in growth. It is structurally related to the sex hormones, but does not produce their actions. The protective action of cholesterol against saponin hemolysis led to therapeutic trials in hemolytic diseases, but the results are not convincing.

Chemical Characters.—Cholesterol is a monatomic alcohol, $C_{27}H_{45}OH$, with the solubility characters of fats. It is therefore but poorly absorbed (Stadelmann, 1898; Klein, 1910). Its oxidation products produce effects (digitalis and saponin) resembling those of bile acids and of the poisons of toads and snakes. Indeed, all these are probably derivatives of cholesterol (Faust, 1911; Flury, 1911).

Occurrence.—Cholesterol is an essential constituent of animal cells, and therefore occurs in most foods. Egg yolk is especially rich, one yolk containing about 0.25 Gm. (Klein, 1910). It is generally prepared from gallstones. Its esters and homologues constitute wool fat (see Index). About three-fourths of the total fat of blood plasma consists of cholesterol esters. Small quantities are present, partly free and partly as esters of the higher fatty acids, in the blood plasma, red corpuscles, and especially in the leukocytes, in fairly constant quantity under normal conditions. Cholesterol plates may be found in any tissue when the cells have undergone slow destruction and where absorption is poor.

Formation of Gallstones.—According to Schade, cholesterol that exists in the bile as a colloidal solution is protected by the cholates, soaps and other constituents. Acidification precipitates the cholesterol by disrupting the protecting salts. Bacteria that produce acid, such as typhosus, pyocyaneus and proteus tend to precipitate the cholesterol, while infections with nonacid-forming bacteria, such as staphylococcus aureus, do not have this tendency (Lichtwitz).

Cholesterol Income.—The cholesterol content of the body is increased by feeding cholesterol (Lehmann, 1914). Mice can *synthesize* cholesterol, probably from intermediates of fat and carbohydrate metabolism, when it is absent from their food (Schoenheimer and Rittenberg, 1938); but higher animals appear to depend chiefly upon the food and therefore eventually on plants. Ordinary food contains adequate amounts; but when the diet is restricted, or when there are extraordinary demands, as in growing children, it may conceivably be deficient (Mendel, 1914).

The liver appears to be the chief site of cholesterol synthesis. Liver slices, but not other tissues, utilize the C atoms of acetic acid or ethanol for cholesterol synthesis (Borek and Bloch, 1946).

Absorption.—Food cholesterol is not absorbed effectively unless fat is also present in quantitative relationship (R. P. Cook, 1937). Other closely related sterols, such as phytosterols, coprosterol and even allo-cholesterol are practically unabsorbable (Schoenheimer *et al.*, 1935). Ergosterol becomes absorbable when changed to viosterol by irradiation. Cholesterol is absorbed from the alimentary tract into the lymph, being demonstrable in the thoracic duct. During absorption from the intestines, free cholesterol is partly esterified, and the esters are partly hydrolyzed (J. H. Mueller, 1915). Illingworth, 1921, reported that it is absorbed from the bile in the gallbladder, but this was denied by Elman and Graham, 1932, who found that the gallbladder secretes cholesterol into the stagnant bile. In cholesterosis of the gallbladder, the bile contained only 0.135 to 1.248 mg. per 100 cc. (McEachern and Gilmour, 1932). *Hypodermic injection* into rabbits produces marked inflammation and necrosis of the subcutaneous tissue. This gradually subsides with the disappearance of the cholesterol, which is effected mainly through the leukocytes (Basten, 1915).

Fate and Excretion.—Considerable cholesterol is destroyed, increasing with the income (Schoenheimer and Breusch, 1933; F. Fitz and Bruger, 1936); a part is excreted into the bile, but is reabsorbed almost quantitatively; a part is oxidized to dihydrocholesterol and excreted by the mucosa of the large intestines, and is there reduced to coprosterol by the fecal bacteria (review, C. F. Bills, 1935). A part of the excess cholesterol is deposited in the tissues, partly as such, partly as esters, the latter especially in the liver (Sperry and Stovanoff, 1935). Cholesterol administered by mouth, as such or as food, produces marked increase in fatty acids and cholesteryl esters in the *liver*. This is prevented by lipocaic and inositol, not by choline.

Blood cholesterol is about equally distributed between the plasma and corpuscles. The normal cholesterol content of human serum ranges between 130 and 220 mg. per 100 cc.; mean, 160. It is not affected by feeding 2 to 10 Gm. of cholesterol. It varies in the same direction as the other lipids of the blood, and is *increased* with diets rich in fats, in diabetes mellitus, icterus, arteriosclerosis, nephritis, alcoholism, anesthesia, pregnancy, syphilis, excision of adrenals, hyperthyroidism. It is *diminished* with diets poor in lipids, by high body temperature, and in cachexias (McEachern and Gilmour, 1932; Cutting and Tainter, 1934). The reasons for these changes are not clear. A part of the blood cholesterol is derived from disintegration of the erythrocytes. Cholesterol probably plays a role in *fat metabolism*, but this is not understood (Bloor, 1917). If cholesterol is injected *intravenously*, it leaves the blood rapidly, and is deposited in various organs, and partly excreted by the intestinal tract and urine (not by the liver; Bentner and Hepner, 1928). The kidneys show degenerative changes and focal infiltration with cholesterol (K. Dewey, 1916).

Atheroma.—Feeding or injections of cholesterol produce arteriosclerotic lesions in rabbits, with deposits of anisotropic lipids in the intima and especially the media of the aorta and less frequently in other vessels (Adler, 1914; Denny and Frothingham, 1914). The deposition of lipids is the result, not the cause, of injury to the media (Duff, 1936). There are also degenerative changes in the suprarenal cortex (Knack, 1915). Less marked arterial changes are produced in guinea pigs (Bailey, 1915). Chicks invariably develop atherosclerosis of the large arteries, including the coronary, if 2 per cent cholesterol is added to their basic diet for six months (Dauber and Katz, 1943). The atheroma in rabbits may be prevented by feeding iodine compounds (J. H. Page and Bernhard, 1935) and by the administration of large doses of choline (300 mg. daily; C. A. Baumann and Rusch, 1938). Lipocaic, which does not affect the level of blood cholesterol in normal rabbits, prevents the rise and the atheroscleroma of high cholesterol diet (M. J. Huber *et al.*, 1937). *Polyvinyl alcohol*, when injected into dogs, induces atheromatosis similar to that of cholesterol. It is attributed to disturbed metabolism of the vascular walls by the physicochemical changes (W. C. Hueper, 1941).

By *intravenous injection* of cholesterol into rabbits over long periods, Adler, 1917, produced arterial lesions closely resembling those of human arteriosclerosis. They were most marked in the pulmonary artery. Adler was inclined to attribute them to the intermittent but extensive blocking of the vessels by the injected oil, and therefore not to the chemical properties of cholesterol.

Arteriosclerosis in man has no relation to the blood cholesterol level (Landé and Sperry, 1936), but hypersensitive patients average a higher cholesterol content in the renal arteries and thoracic aorta. This increases with age (Bruger and Chassin, 1941). Increase of the cholesterol blood level may favor the development of *senile atherosclerosis*, but it may be absent in the spontaneous disease. The fatty deposits in the intima of the arteries often have the same lipid composition as in the blood plasma and normal intima (review, E. F. Hirsch and Weinhouse, 1943).

Xanthoma.—Young rabbits on diets containing one-fourth per cent of cholesterol for six to ten months develop xanthomas in the subcutaneous tissue of the feet. The tumors averaged 46 per cent of fat, and 4.6 per cent of total cholesterol, in the dry weight. The cholesterol level of their blood averaged 6.2 mg. per cubic centimeter, the controls averaged 1.4 mg. (Rusch *et al.*, 1939).

Effects on Cancer.—The injection of cholesterol emulsions was reported to accelerate the growth of experimental cancer (Burnett, 1913) and to promote the formation of metastases, but it does not originate cancers, or increase the rate of natural incidence.

Effects on Growth.—Sperry and Stovanoff, 1935, found that the slowed growth of rats with long-continued cholesterol feeding is associated with diminished consumption and utilization of food. They believe this related to the large deposits of cholesterol esters in the liver.

Protection against Poisons.—Free cholesterol neutralizes a number of poisons, especially hemolytic (saponin, tetanolysin). *The antihemolytic action* is not very potent. Saponin hemolysis is retarded only if relatively large quantities remain in contact for a considerable time before the erythrocytes are added. Cholesterol retards bile salt hemolysis as does lecithin. It does not materially hinder the action of sodium oleate, or cobra, vibrio and streptococcic hemolysins (Roy and Biswas, 1943). The phenomena are quite complex (J. S. Lee and Tsai, 1942). It is also said to protect against strychnine, but only if the two substances are mixed (Fizzoni and Perucci, 1919). It is reported to be somewhat stimulating to the *heart muscle* (Danilewsky, 1907).

Therapeutic Uses.—The protection against hemolytic poisons suggested the trial of cholesterol in pernicious anemia (Reicher, 1908), and in paroxysmal hemoglobinuria (Pringheim, 1912 and 1913), but it did not prove successful. The dosage was six intramuscular injections, on alternate days, each of 5 cc. of 10 per cent cholesterol emulsion; or by mouth, 3 Gm. in 100 cc. of olive oil, daily, in tablespoon doses. The preparation of a watery emulsion for intravenous injection was described by Dewey, 1916. Cholesterol is official in the U.S.P.

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LECITHINS

Lecithin was exploited as a "tonic," but it did not achieve a place in therapeutics. The ordinary diet furnishes a liberal supply of lecithins, and the small quantities that may be added in the form of rather expensive medicines could only have imaginary effects.

Chemical Structure.—Lecithins are esters of fatty acids, glycerophosphoric acid, and a nitrogenous base (mainly choline). The various lecithins differ according to the fatty acid and the base. They occur in animal (not in vegetable) cells, generally combined with proteins. Their place may be taken by related compounds or "phosphatides," which are but little understood. Lecithins are conveniently isolated from brain substance or egg yolk ("vitellin"). The commercial products are quite impure. They contain 3.84 to 4.12 per cent phosphorus. H. MacLean, 1915, states that ordinary lecithin is a mixture of cephalin, which tends to become insoluble in alcohol, and true lecithin, which remains alcohol soluble.

Properties.—Lecithin is a white to orange colored substance, usually amorphous and waxy when dry. It is hygroscopic, softening to a semifluid mass in the air. It also oxidizes readily, becoming darker. It dissolves in alcohol or most fat solvents (not in acetone). It is insoluble in water, but readily takes up water, swelling to a gelatinous mass and finally to a colloidal solution, from which it is precipitated by certain acids and salts; while other salts prevent the precipitation (W. Koch). It is decomposed by prolonged contact with water; alkalis saponify it readily into choline, fatty acid and glycerophosphoric acid. Further cleavage results in ordinary phosphoric acid. The cleavage with dilute acids is quite slow.

Cephalin is a highly unsaturated monamino-monophosphatide. Its nitrogenous base is probably not choline; otherwise it is closely related to lecithin. Koch and Woods, 1915, believe that it is distributed as widely as lecithin. The number of *other phosphatides* is probably limited, the various phosphorized fats prepared from different tissues being probably mixtures of lecithin and cephalin, with closely related homologous fragments (Levene and Komatsu, 1919). *Plant phosphatides* were formerly considered identical with lecithin, but are now known to be quite distinct. They usually contain a sugar molecule.

Phytin consists of the salts (usually calcium) of an organic phosphoric acid, probably containing inosite (presumably inosite-hexaphosphoric acid). It is widely distributed in plants (bibliography, A. R. Rose, 1912). It is absorbed and metabolized, but must be decomposed before it can be used by the tissues. Abundant amounts are contained in ordinary food, and there is no clear evidence that it is superior to inorganic phosphates.

Lecithin Content of Food.—The ordinary mixed diet contains at least 5 Gm. of lecithin daily; and this can be doubled by adding two eggs (egg yolk contains 6.8 per cent of lecithin), or liver or sweetbreads, which are also rich in phosphorus. Milk is rather poor in lecithin (a pint contains 0.3 to 0.4 Gm.; W. Koch, 1905).

Fate of Lecithin.—Little, if any, lecithin is absorbed as such; the fat-splitting enzymes of the intestines split off the glycerophosphoric acid, which is further decomposed into phosphoric acid before it is absorbed (Bokay, 1877; Plimmer, 1913). Possibly a fraction of the glycerophosphoric acid, and even of undecomposed lecithin, is absorbed before the cleavage is completed. In this case, or if the lecithin is introduced parenterally, the cleavage occurs in the tissues; the excretion is entirely as inorganic phosphates.

Synthesis.—Lecithin is readily synthetized in animals from inorganic phosphates, for when radioactive phosphate is administered it can soon be demonstrated in the phospholipids (Hevesy and Lundsgaard, 1937). The lecithin synthesis occurs chiefly in the liver; some also in the intestinal cells with phosphorylation of fatty acids as intermediate (review, A. C. Frazer, 1940). Roehmann, 1908, showed that mice can be maintained for two generations on lecithin-free food.

The functions of phospholipids are obscure, although the presence of considerable quantities in all the tissues indicates that they are important. It has been suggested that they are intermediates in the metabolism of fatty acids; that they act as acceptors of oxygen and hydrogen through their double bond linkage; and that the peculiar physical and solubility properties are essential to cell structure; but none of the suggestions are proved (review, Sinclair, 1934).

Nutrition and Growth.—The statements of different investigators are so contradictory as to indicate that the effects of phosphatide administration are unimportant; and this would be expected, since animals are able to synthesize all the lecithin they require. The subject is reviewed by Forbes and Keith, 1914. Best and Campbell, 1936, found that feeding or injecting lecithin diminishes the deposition of fat in the liver, in phosphorus poisoning, or when a large quantity of fat is fed; but this effect is due to the choline. Danilewsky, 1895 and 1896, reported that feeding isolated lecithin stimulates growth, increases the red corpuscles and accelerates physical development, as compared with control animals; but others (Goldfarb, 1907; Yoshimoto, 1910) failed to obtain any results. The clinical data are even more unsatisfactory than the experimental.

Phosphorus in Nerve Tissue.—Nervous tissue is rich in phosphorus (⅓ per cent of moist; 1½ per cent of dry), but not more so than glandular organs. Its phosphatide content (27 per cent of dry) is three times or more that of glands; but the presence of phosphorus is not decreased even in severe nervous diseases (dementia praecox) (W. Koch, 1909).

Carcinoma.—Hypodermic injection retards the growth of rat carcinoma; oral administration is not effective, presumably because the lecithin is decomposed before absorption (Robertson and Burnett, 1916).

Action on Circulation.—Danilewsky, 1906, and Katznelson, 1910, state that the heart of frogs and rabbits is stimulated by dilute, depressed by concentrated solutions. Lifschitz, 1910, describes rise of blood pressure and cardiac stimulation. Lawrow and Woronzow, 1912, reported a marked antagonistic effect to cardiac poisons (chloral and other lipolytic narcotics). They attribute the effects partly to direct cardiac stimulation, partly to disintoxication of lipolytic poisons. Hauschmidt, 1913, confirms that intravenous injection is harmless and lessens the toxicity of the lipolytic narcotics and also of curare, strychnine and morphine; but that it increases the toxicity of ricin. G. K. Ashby, 1946, confirmed that intravenous injection of pure lecithin is not toxic to rabbits, but that it becomes so on exposure to air. Commercial samples were toxic.

Hemolysis.—Minute quantities of lecithin markedly accelerate some hemolytic poisons, but not others. This is due to contamination with free fatty acids and does not occur with pure lecithin (Roy and Chopra, 1941). Complex *antihemolytic* properties of lecithin and cholesterol are described by Lee and Tsai, 1942.

Role in Fat Assimilation.—Bloor, 1915 *et seq.*, found that the *lecithin content of the blood* increases 10 to 35 per cent during the absorption of fats, generally parallel to the increase of blood fat. The accumulation of lecithin is greatest in the corpuscles, which contain about twice as much as the plasma. The cholesterol content (which is about equal in the corpuscles and plasma) is not increased by feeding fats.

Lecithin on Cutaneous Absorption.—Borshim, 1912, claimed that small amounts, rubbed into the skin before the application of a potassium iodide solution, increase its absorption; while large amounts have the reverse effect. Glucose, salicylic acid and tetanus toxin were not absorbed.

Administration.—Commercial lecithin has been administered as pills, 0.1 to 0.5 Gm. per day. It has also been given hypodermically, 1 cc. of 5 per cent in oil; but in view of the impurities, this is not advisable. It is incompatible with alkalis.

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VITAMINS

In addition to the essential calories, amino acids and inorganic salts which are needed in considerable quantity to replace the ordinary daily wear, normal metabolism also requires the presence of minute amounts of various other elements, inorganic and organic, probably as essential parts of specialized enzyme systems. This holds true of all living organisms, the lowest plants—such as yeast—as well as of the higher animals.

Small quantities of such substances are often sufficient. "Biotin," for instance, acts on the growth of yeast in a dilution of $1:4x10^{11}$ (F. Kogl, 1937). Yeasts, molds and bacteria are specific in their nutritive requirements, so that they are utilized for the assay of vitamins and amino acids (references, J.A.M.A., 1944, *124:*578, 649). The *intestinal bacteria* synthesize a number of vitamins, particularly B and K. Interference with the intestinal flora by effective intestinal antiseptics, such as sulfaguanidine and succinyl sulfathiazole, hinders the growth of rats (C. A. Elvehjem, 1944). The needs of *insects* appear even more specialized than those of man, perhaps because their power of synthesis is more limited (review, C. M. McCay, 1938).

The term "*vitamin*" was introduced by Casimir Funk, 1911, for these indispensable "accessory food substances" (Gowland Hopkins, 1912) which vertebrates can not synthesize for themselves, at least in adequate quantity, and which they must obtain from food. They are definite organic substances, generally non-nitrogenous hydrocarbons, belonging to various chemical groups. Some have been isolated as pure crystals and prepared synthetically, and these have identical actions. They are rather unevenly distributed among various animal and vegetable foodstuffs, so that deficiencies are liable to occur with one-sided diets, although varied diets generally furnish adequate supplies, even to the poorer families. Deficiencies may arise from digestive disturbances which interfere with proper absorption, and sometimes from unusual demands (McCollum and Simmonds, 1929; "vitamin deficiency by interference," N. Jolliffe, 1943). *Starvation* in itself automatically cuts off the supply of vitamins, so that vitamin deficiency becomes a part of malnutrition generally, in chronic diseases, marasmus, chronic intoxications and drug addictions. The *restricted diets* in the treatment of obesity, allergy, infections, convalescence, peptic ulcer and infant feeding generally require supplemental administration of vitamin mixtures. The *time of development* of the deficiency varies for each substance and differs for various animals, according to their need for the particular vitamin, the amount stored in the tissues, and their ability to synthesize. The store of thiamine is exhausted in a week or two; that of ascorbic acid lasts for several months.

Suboptimal Diets.—From an investigation of Americat dietaries, Borsook and Halverson, 1939, concluded than practically all families spending $2.08 per week per person on food were eating adequately, and some with $1.50. In families with yearly incomes of less than $3000, practically all consumed enough vitamin C, ⅔ were deficient in vitamin B, practically all did not consume enough vitamin A, and half not enough Ca. Practically all had sufficient Fe.

Deficiency in the supply of a specific vitamin results in the specific syndrome of the "vitamin deficiency disease," such as rickets, scurvy, beriberi, polyneuritis, xerophthalmia, pellagra, which are characteristic for each vitamin; and in nonspecific general impairment of appetite, nutrition, growth, fertility, general health and resistance to infections. It is through these deficiencies, and their prevention and cure by certain foods, that the existence of the various vitamins was recognized. Before the vitamins were isolated, they were distinguished by the letters of the alphabet: (A) for the antixerophthalmic vitamin; (B_1) for the antineuritic thiamine chloride; (B_2) for the antipellagric nicotinic acid; (C) for the antiscorbutic ascorbic acid; (D) for the antirachitic vitamin; and so on. These designations continue to be used as synonyms of the pure chemicals or of the groups of related chemicals which share the actions. A tabulation of the symptoms and treatment of vitamin deficiencies is published by the Committee on Foods and Nutrition, 1946, J.A.M.A., *131*:666.

The *nonspecific effects* are chiefly manifestations of disturbed nutrition, which necessarily interfere with *growth* and general resistance, so that the organism is more susceptible to *infections*. Even the dermatoses are merely conspicuous instances of what occurs in other cells (R. J. Williams, 1942). The general impairment of nutrition probably accounts for decreased fat absorption when A, B or D vitamins are notably deficient (review, A. C. Frazer, 1940). Deficiencies of vitamins lower resistance to the progress of rat leprosy (Badger *et al.*, 1940).

The mode of action of vitamins is generally that of coenzymes, the simpler parts of special enzyme systems (review, C. A. Baumann and Stare, 1939). Thiamine pyrophosphate is cocarboxylase. Nicotinic acid amide and riboflavin "lubricate" oxidative processes. Riboflavin phosphoric acid is the prothetic group of flavoprotein, the "yellow enzyme" which is an essential part of many dehydrogenation systems (review, Baumann and Stare, 1939, "Respiratory Enzymes").

Vitamin deficiency by substitution may be produced by chemicals so closely related to a specific vitamin that they compete with it in its enzyme relations without producing its specific reactions. Administration of glucoascorbic acid produces scurvy; pyrithiamine produces all the phenomena of thiamine deficiency; dicoumarin those of K vitamin deficiency; phenazine of riboflavin deficiency; beta acetylpyridine of nicotinic acid deficiency (review, D. W. Wolley, 1944).

The tissue changes in vitamin deficiencies are reviewed by Wolbach and Bessey, 1942.

Multiple Factors.—Unsuitable diets are likely to be deficient in more than one factor, so that clinical vitamin deficiencies are usually more complicated than the experimental. Pellagra generally involves deficiency of nicotinic acid, thiamine chloride, riboflavin and others. Each contributes to the syndrome, which is not completely curable until each of these has been met.

Single deficiencies occur clinically in rickets and in infantile scurvy.

Vitamin mixtures should represent simple multiples of the normal requirements. The U.S.P. provides a series of *official multiple-vitamin preparations* under the name of "*Triasin B*" capsules, tablets and injections containing thiamine, riboflavin and nicotinamide; and "*Hexavitamin*" tablets and capsules containing A and D vitamin, ascorbic acid, thiamine, riboflavin and nicotinic amide.

The composition of these is shown in the following table, along with the daily normal income recommended by the National Research Council, and the *Minimum Daily Income* recognized by the Food and Drug Administration.

	Minimum Daily Requirement (F.D.A.)	Recommended Total Daily Income (NRC)	Hexavitamin Capsules and Tablets	Triasyn B Capsules and Tablets
Vitamin A	4000 units	5000 units	5000 units	———
Vitamin D	400 units	400 to 800 units	400 units	———
Thiamine hydrochloride	1 mg.	2 mg.	2 mg.	2 mg.
Riboflavin	2 mg.	3 mg.	3 mg.	3 mg.
Nicotinic acid amide	10 mg. (?)	20 mg.	20 mg.	20 mg.
Ascorbic acid	30 mg.	75 mg.	75 mg.	———

Supernormal income of vitamins, as additions to the usual American diet, produces no recognizable effect on resistance, energy, "vim" or anything else except the imagination (Ruffin and Cayer, 1944). There is no satisfactory evidence that it improves the output of factory workers (A.M.A. Committee on Foods, 1942, J.A.M.A., *118*:618). The incidence of colds is not reduced by multiple vitamins (Cowan *et al.*, 1942). The vast sums expended on vitamins by the public are largely wasted.

The healing of wounds is not improved by topical applications of any or all of the vitamins; or of sulfonamides (rats; Williams and Bissell, 1944).

Excessive vitamin income appears capable of increasing the virulence of certain *virus infections* (report, Council on Pharmacy and Chemistry, 1945, J.A.M.A., *129*:211). *Deficiency of vitamin income* increases the normal resistance of mice to inoculation of poliomyelitis virus (C. Foster *et al.*, 1942). Undernourished chickens are practically immune to the Rous sarcoma virus (Rous, 1911). Caution is indicated in transfering these results to man. The relation of vitamins and hormones to cancer are reviewed by D. Burk and Winzler, 1944.

Absorption.—All vitamins are absorbable from the *alimentary tract* under normal contions; but mineral fats interfere with the absorption of the fat soluble vitamins, especially A and carotene. Bile is essential for the absorption of vitamin K. The *skin* absorbs the lipid-soluble vitamins A, D and K; D sufficiently to produce curative and even fatal effects; but the absorption is inexact and uneconomical. It is doubtful whether the water-soluble B and C vitamins are absorbed through the skin (reviews, H. A. Calvery *et al.*, 1946; Eller and Wolff, 1940).

Administration. — Vitamin deficiencies should be prevented and corrected by suitable diet. Concentrates or isolated principles, however, make it possible to introduce additional quantities when they are especially needed, as in infant feeding, or to meet acute symptoms, or when absorption is impaired. The dosage of the pure principles should be prescribed as milligrams; the impure preparations as U.S.P. units.

Quantitative determinations of the vitamins generally require biological methods, the prevention or cure of experimental deficiencies. The potency may be expressed in arbitrary units. Comparison standards for A, B, C and D are furnished by the Health Organization of the League of Nations and designated as *International Units.* The U.S.P. units conform to these.

ASCORBIC ACID

This constitutes the *Vitamin C* or *antiscorbutic vitamin* (*cevitamic acid*). It occurs widely distributed in plants and animal tissues, and therefore in fresh food, but is easily destroyed by oxidation and is therefore likely to be deficient in preserved foods. It is a dietary essential for man, primates and guinea pigs, but most other animals synthesize it in adequate quantity. It is a fairly simple carbohydrate, related to the sugar sorbose, which occurs abundantly in fresh fruits and vegetables, and to a less extent in meats. It is also prepared synthetically. Its deficiency leads to the symptoms of scurvy, with hemorrhages from the gums and in other situations, changes in tooth and bone formation, suspension of growth and other phenomena; these are promptly corrected by its administration. The condition is not infrequent in improperly fed infants. Cows' milk contains only a fourth as much as human milk. Severe scurvy was common on ships in the days of long sailing voyages. It is now rare in adults, because these have considerable of the substances stored in their tissues so that the disease develops only after a deprivation of some four months, for which there is not often occasion. Partial deficiency of ascorbic acid may lead to a variety of "prescorbutic" phenomena, including dental caries, pyorrhea and gum infections; but these are not characteristic and may arise from other causes. Various forms of clinical gingivitis are not improved by administering ascorbic acid (Stamm *et al.*, 1944). The daily requirement of ascorbic acid is not definitely known, but it increases in pregnancy and lactation, and with heightened metabolic activity such as heavy manual labor, and in fever, especially in tuberculosis.

Historical.—The first successful antiscorbutic treatment is ascribed to Jacques Cartier, 1536, who employed an infusion of pine needles in an expedition on the St. Lawrence River. The real knowledge of scurvy protection dates from Lind, 1747, a British naval surgeon, who demonstrated the efficacy of lemon juice. Experimental investigation was made possible when Holst and Fröblich, 1907, found that scurvy could be induced in guinea pigs by a diet devoid of green food. C. G. King and Waugh, 1932, first isolated crystalline hexuronic acid from lemons and identified it as the antiscorbutic active principle. Two weeks later, Svirbely and Szent-Györgyi announced that they had isolated an active hexuronic acid from adrenal glands. Waugh and King then showed that the active hexuronic acid from the two sources is identical. The hexuronic acid had been prepared by Szent-Györgyi in 1928 from several sources, but without his knowing its relation to scurvy (C. G. King, 1938). Karrer *et al.*, 1933. and Haworth, 1933, established the correct formula by synthesis. It is a levorotatory lactone of tetraoxyketocapronic acid. It was named "ascorbic-acid" by Haworth and Szent-Györgyi, 1933.

Related Compounds.—Dextro-ascorbic acid has no antiscorbutic action. Its aqueous solution oxidizes more rapidly than the levo form and therefore tends to protect the latter from oxidation (Yourga *et al.*, 1944). Levo-rhamno-ascorbic acid has about a fifth of the potency of ascorbic acid; none of the other derivatives ranks higher than a tenth (Zilva, 1935).

The assay methods are reviewed by Bessey, 1938. The *chemical assay* of ascorbic acid by titration of its reducing action, under specified conditions, with 2.6 dichlorophenol indophenol as indicator, is more rapid and accurate, although less specific than the biological methods. The *international unit* is 0.05 mg. of ascorbic acid, the amount usually present in 0.1 cc. of lemon juice. Fresh orange juice contains about 1000 units (50 mg.) per 100 cc. The *bio-assays* include the preventive method of Sherman *et al.*, which is probably the most useful; the curative method of L. J. Harris *et al.*; and the dental method of Höjer.

Ascorbic acid is synthetized by most animals, but not by man, the primates and the guinea pig, either adult or embryo. These derive their supply entirely from the food. Dogs, cows, rabbits, rats, mice, prairie dogs, pigeons and chickens are able to supply their own needs without extraneous addition; dogs, indeed, form it considerably in excess of their needs. Mannose is the most effective precursor (S. S. Ray, 1934), but mice and rats use dextrose (Widenbauer and Korschorreckt, 1937). Rats require adequate intake of *thiamine and riboflavin* for their ascorbic synthesis (Sure *et al.*, 1943). Dogs on thiamine-deficient diets develop oral scorbutic lesions which are prevented and promptly cured by thiamine administration (Govier and Greig, 1943). Adrenalectomy has no effect on the synthesis. Chick embryos synthesize early (King, 1938, review). *Ether anesthesia* increases the synthesis by ten to fifteen times in dogs, considerably in rats, but not in guinea pigs (D. E. Bowman, 1932).

The formation of ascorbic acid in plants is apparently associated with growth, for it is abundant in the actively growing parts of all green plants, including algae and perhaps bacteria. It is considerably more abundant in green leaves than in colorless leaves or roots, suggesting a relation to chlorophyll. It is often associated with carotene, but not necessarily. Unripe seeds, such as green peas, contain large amounts, which decrease as ripening advances. Dry seeds contain neither ascorbic acid nor its oxidation product, dehydro-ascorbic acid; but when they are moistened and warmed, ascorbic acid appears in a few hours in the area of sprouting (reviews, C. G. King, 1936, 1938).

Absorption.—Ascorbic acid is readily absorbed from the intestinal tract in the amounts in which it is administered. It is subject to bacterial decomposition in the intestines, and it is conceivable that abnormal decomposition may account for some cases of deficiency. It is protected by even small amounts of dextrose (A. I. Kendall and Chinn, 1938).

Fate.—The absorbed ascorbic acid is partly distributed and stored in the tissues, partly excreted unchanged, especially in the urine. and a considerable part is destroyed, it is not known where or how. The loss is greater during rapid growth, in both plants and animals (M. E. Reid, 1943). The retention depends on the need of the organism and the degree of saturation of the storage depots. The *quantity destroyed* corresponds to the difference between the income and excretion, and, when these are in equilibirum ("saturation balance"), amounts to 25 to 50 mg. per day in man (King, 1938).

Oxidation.—With *p*H below 7.6, aqueous solutions are not oxidized in the air unless a catalyst is added. The solutions are therefore not auto-oxidizable within the normal *p*H range of animal or plant tissues (Barron *et al.*, 1936), but in plants ascorbic acid occurs associated with specific *ascorbic oxidase*, which catalyzes its oxidation. It may also be oxidized by phenol oxidases, by peroxidases, by hemochromogen and by traces of copper (review, Lipton, 1942). Its role in *cell oxidation* is obscure, although it is presumably concerned in respiration. It is conceivable that activated reactions occur to enable ascorbic acid to act as a hydrogen transport agent and respiratory catalyst, and as a reversible oxidation-reduction system with its immediate oxidation product, dehydroascorbic acid VII; but this has not been demonstrated (King, 1938). For instance, liver and kidney tissue of C-depleted guinea pigs does not show any decrease of respiratory capacity, nor is it increased by adding ascorbic acid (Stotz *et al.*, 1937). It appears to be essential only for the metabolism of phenylalanine, phenylpyricoic acid and l-tyrosine (Basinski and Sealock, 1946). Glutathione protects ascorbic acid against oxidation, and ascorbic acid protects epinephrine. Certain acids and potassium *thiocyanate* and *iodide* protect ascorbic acid solutions against oxidation, by forming addition or condensation products. Ascorbic acid *detoxicates* cyanide and phenol analogous to glycouronic acid (Leibowitz and Guggenheim, 1938).

The excretion of ascorbic acid occurs chiefly in the urine. In man, this ordinarily contains about 35 mg. per day. A daily output of less than 10 to 15 mg. indicates deficiency. Scorbutic children excrete less than the normal (Harris and Ray, 1935), reflecting their subnormal income. If an additional quantity is ingested, the concentration in the urine rises, reaching a maximum in three to six hours, up to eight or ten times the normal (L. J. Harris *et al.*, 1933).

If it is administered daily in graded doses over long periods, the urinary concentration is fairly proportionate to the intake, and nearly identical for different individuals; but if only a few doses are given, different individuals vary in the amount excreted. The urinary excretion after a single adult dose of 600 mg. is used as a clinical test of the repletion or depletion of the ascorbic acid store; excretion of less than 30 per cent in twenty-four hours is below normal (Harris and Ray, 1935).

The fecal excretion is slight, normally less than 6 or 10 mg. per day in man, even when large amounts are ingested. It is increased in diarrhea (Farmer and Chinn, 1938).

Conditions other than storage also affect the output. Fever, for instance, causes it to drop, and additional income is required. *Acetylsalicylic acid* in therapeutic dosage increases the ascorbic acid excretion of children to two or three times (A. L. Daniels and Everson, 1939). This effect occurs in rats and guinea pigs, also with sodium salicylate, but not with neocinchophen, caffeine, salyrgan or sodium bicarbonate (L. T. Samuels *et al.*, 1939). The marked increase after ether anesthesia of dogs and rats is due to increased synthesis. Many terpenes and sesquiterpenes, including camphor, carvone, menthol and thujone, increase ascorbic acid in rats, apparently by increasing synthesis (Longenecker *et al.*, 1939), perhaps to detoxicate these by conjugation.

The blood concentration of ascorbic acid is an index both of its availability and of its storage. In human serum it ranges ordinarily between 0.6 and 2 mg. per 100 cc., averaging about 1.2 mg. in normal, 0.8 in prescorbutic and 0.5 in clinical scurvy (King, 1938). It is inverse to the amount required to produce saturation, as reflected in the urine excretion (Smith, 1938). With a *diet free from ascorbic acid*, the plasma level of man falls to practically nothing in about forty-two days. Symptoms of scurvy appear in five months and become severe in six months (Lund and Crandon, 1941). The plasma level of ascorbic acid is reported to be decreased by administration of neoarsphenamine, and more markedly by iron; bismuth has no effect (Farmer *et al.*, 1940). It is significantly changed by inducing *hyperpyrexia* in normal human subjects (S. L. Osborne and Farmer, 1942).

Storage in Organs.—Ascorbic acid occurs in all tissues and fluids. The amount varies with individuals (King, 1934), but the relative order is the same in all vertebrates, whether they synthesize the substance or obtain it from the food. The total amount is probably highest in the liver (Zilva, 1936); but the concentration is generally highest in the tissues with the highest metabolic rate. The pituitary gland is especially high (2.6 mg. per Gm. in the pars intermedia); then generally, in descending order, in the corpus luteum, adrenal cortex, young thymus, liver, brain, testes, ovaries, spleen, thyroid, pancreas, salivary glands, lung, kidneys, intestines, heart muscle, spinal fluid and blood; the concentration in the heart is about a twelfth of that in the adrenals (Yavorsky *et al.*, 1934). Active tumor tissue ranks high, decreasing with necrosis. The organs of the newborn have a high concentration which gradually decreases while on *milk income*, faster on diluted cows' milk than for the breastfed. The daily excretion of breastfed infants in early lactation is 40 to 50 mg. of ascorbic acid. Human milk contains 4 to 8 mg. per 100 cc., raw cows' milk 1 to 2.6 mg., pasteurized milk 0.1 to 1 mg. (King, 1938, review).

The deficiency phenomena have been explained as inability of the mesenchymal supporting tissues to form and maintain their characteristic intercellular substance (in contrast to vitamin A, which acts on ectodermal and endodermal cells). The defect involves the collagen of the fibrous tissue, the matrix of bone, dentine and cartilage, and all nonepithelial cement substance, including that of the vascular endothelium. This leads to structural weakness, to hemorrhage in regions of stress and trauma, to failure to form osteoid tissue, to loosening of the teeth, to delay of wound healing, and the like. The calcium metabolism is not affected directly, but in advanced scurvy calcium is liberated by the osteoporosis. The proliferative power of the cells is not impaired, and the osteoblasts undergo their normal morphologic changes. Connective tissue cells continue to manufacture an imperfect and often liquid substance, but this does not form fibrils. Administration of ascorbic acid rapidly converts the liquid into the normal intercellular jell. Improvement is demonstrable within twenty-four hours. The ascorbic acid is evidently involved in some obscure manner in the synthesis of collagen and reticulin. Tissue culture experiments have given conflicting results (Wolbach and Howe, 1926; Dalldorf, 1938; Wolbach and Bessey, 1942; M. E. Reid, 1943).

D. L. Maclean *et al.*, 1939, do not believe that organs other than the teeth and bones show sufficient change to justify a general gelation defect theory, but that there is primary degeneration of the odontoblasts and osteoblasts.

Capillary vulnerability is the most obvious symptom of scurvy. If the teeth are erupted, the *gums* become swollen, boggy, hyperemic, bleed easily, ulcerate and necrose. The capillary bleeding is probably due to weakness either in the endothelial cement substance or in the support of the collagen fibrils. (The *effect of dietary deficiencies on oral structures* is reviewed by Schour and Massler, 1945.) The *skin* also shows early perifollicular or petechial hemorrhages, especially in the lower extremities and where it is exposed to pressure. The earliest indication of incipient scurvy is the "capillary resistance test," the production of petechial hemorrhages by venous stasis (Göthlin, 1933, 1937; Dalldorf, 1933). Severe scurvy interferes with the healing of wounds (Lund and Crandon, 1941). Ascorbic acid is not effective against hemorrhagic conditions other than scurvy (review, Witts, 1937). *The dental effects of scurvy* have been studied extensively on the growing teeth of guinea pigs. Ascorbic acid deficiency arrests the formation of dentine by the odontoblasts and the separation of the pulp. This is the basis of one of the bio-assays. There are no corresponding data, however, for human infants; and it would not affect teeth that have erupted (Wolbach). The assertion that *dental caries* is a manifestation of latent scurvy (M. T. Hanke, 1930) is not supported by good evidence; nor is there convincing proof of its causation by deficiency of vitamins A and D. The original studies of Howe *et al.* on tooth changes were erroneous (Wolbach and Bessey, 1942). *Bone formation* ceases in the diaphyses of the long bones, and the existing bone becomes rarefied. The epiphyses are generally not affected. The periosteum shows abnormal connective tissue with tendency to subperiosteal hemorrhages (Dalldorf). Ascorbic acid combines readily with *calcium* and with protein, the latter much more readily if calcium is present (Ruskin and Jonnard, 1938). Josephson, 1935, reported that ascorbic acid tends to clear up clinical *cataracts*, especially those following dinitrophenol administration, and also dinitrophenol neuritis. Hawley and Pearson, 1938, find the ascorbic acid content lower in cataract lens, although the blood level is generally normal. They suggest that the lowered content of the lens may be the result rather than the cause of the cataract. Marked acceleration of the growth of implanted *carcinoma* in mice has been reported to follow administration of the ascorbic acid (Fodor and Kunos, 1934).

Metabolism, Nutrition and Growth.—Ascorbic acid is a potent stimulus to the growth of plant embryos that have been separated from the reserve food supply of the seeds. It is quite probable that it enters directly into the metabolism of animals, but the evidence is meager. Deficiency interferes with growth, but this could be explained by its effect on bones, connective tissue and capillaries. Sigal and King, 1936, reported that the ability of guinea pigs to assimilate dextrose orally is gradually impaired by ascorbic deficiency. Intravenous injection of large doses does not change the blood sugar level, however, nor that of cholesterol, calcium or phosphate; nor does the oral administration of large doses, to 6 Gm. daily, alter the cystine excretion in cystinuric subjects (J C. Andrews *et al.*, 1938). Ascorbic acid administration to rats increases the diabetogenic action of alloxan, under certain conditions (S. Levey and Suter, 1946). *Anemia* by deficient hematopoiesis is common in scurvy, but may be due to other concurrent dietary deficiencies, especially iron (Abt and Farmer, 1938). Ascorbic acid administration prevents the *hyperpyrexia* of dinitrophenol, thyroxin and external heat, but not that of tetrahydronaphthylamine or protein injection (H. T. A. Haas, 1939).

Adrenal Cortex.—Although this contains a rather high concentration of ascorbic acid, there is no evidence of any functional relation. Depletion of ascorbic acid does not shorten, nor its administration prolong, survival after excision of the adrenals (Firor and Grollman, 1934). It has been reported that its administration decreases *skin pigmentation* of Addison's disease, and that large doses produce mottled depigmentation of Negroes, and this has been linked with the observation that it prevents blackening of skin sections by dioxyphenylalanine ("Dopa"); but further experience is needed (Abt and Farmer).

Thyroid administration to guinea pigs raises their requirements of ascorbic acid (Demole and Ippen, 1935). Administration of ascorbic acid protects guinea pigs against thyroid hypertrophy when pituitary thyrotropic factor is injected (Marine *et al.*, 1934).

Resistance to Infection.—A. F. Hess, 1917, pointed out the high incidence of infection in scurvy, which was confirmed experimentally on guinea pigs by G. M. Findlay, 1923. Conversely, infections bring out latent scurvy (Mettier *et al.*, 1930). Wound healing is also impeded by ascorbic deficiency (Lanman and Ingalls, 1937), but the average person has sufficient ascorbic acid income, and further increase does not have a significant effect (Bartlett *et al.*, 1942). These defects are in part common to all nutritional disturbances and in part to the special lesions of scurvy. They are reinforced by the greater need of ascorbic acid when metabolic demands are increased. In active tuberculosis, for instance, the daily human requirement is raised from the normal of 15 to 30 mg. per day to 55 to 140 or even 200 mg. (Heise and Martin, 1936). Low blood values of ascorbic acid have been reported for achlorhydria (Alt *et al.*, 1937) and peptic ulcer; but this may be due to the restricted diet. *Tetanus toxin* is inactivated by ascorbic acid *in vitro*, but apparently not in living animals (Jungeblut, 1937). King *et al.*, 1935 and 1938, reported protection of guinea pigs. It occurs by direct interaction, probably through peroxide produced in the auto-oxidation of ascorbic acid, and is limited to relatively small doses of the toxin (C. W. Jungeblut, 1941). Additional ascorbic acid does not confer protection against *trinitrotoluene* (von Oettingen *et al.*, 1944).

The hemolytic complement activity of serum increases with its content of ascorbic acid to an optimum of about 1 mg. per 100 cc. This holds true for all animals tested, including man, and for variation produced by administration or depletion, including clinical scurvy, or by etherization. The effect occurs also on the addition of ascorbic acid to serum *in vitro*, and is due to the protection of the complement against oxidation: Complement is inactivated by a variety of oxidizing agents, iodine, peroxide, quinone or oxygen, and restored by reducing agents, such as ascorbic acid, hydrogen sulfide, glutathione, sodium hydrosulfite or cyanide. Iodoacetate also inactivates complement and is reversed by ascorbic acid and glutathione, but not by hydrogen sulfide or by cyanide (Ecker *et al.*, 1938, 1939). Ascorbic acid protects *epinephrine* against oxidation and in this way potentiates its pressor action (Reiser, 1938).

Large doses of ascorbic acid are somewhat *diuretic* (W. Evans, 1938), resulting clinically in slowly progressing dehydration (Abbasy, 1937), but with ordinary doses the diuresis is slight and does not appear practically important (C. F. Shaffer, 1944). Several writers have reported *vagotonic symptoms* in children and infants on large doses of ascorbic acid, but these effects do not occur regularly. *Intravenous injection* of 2.3 to 33 mg. per Kg. into chloralosed dogs generally causes prolonged contraction of the spleen, with little or no change in blood pressure (Cioglia and Frada, 1938). In cats, 50 mg. per Kg. lowers the blood pressure more than an equivalent amount of acetic acid (Kreitmair).

Perfusion of the *isolated frog heart* with levo ascorbic acid, 1:10,000, increases the height of contraction, and terminates in systolic arrest after one or two hours. This is not a direct effect, but may be attributed to the cardiac action of hydrogen peroxide which is formed in the oxidation of ascorbic acid, since it is not observed if the oxidation is prevented (Krayer *et al.*, 1943).

Ascorbic acid has been advised clinically for *prophylaxis against poisoning* by metals, organic solvents, aniline derivatives, phenol, cyanides and other poisons. The evidence is unsatisfactory (report, Council on Foods, 1942, J.A.M.A., *118*:620). It has no definite effect on *arsenical dermatitis* (McDonald and Johnson, 1941). It is reported to protect guinea pigs against *liver damage from hydrazine* (K. H. Beyer, 1942). Large doses lower the methemoglobin concentration in *congenital idiopathic methemoglobinuria* by substituting for the deficiency in the natural reducing system (R. F. Sievers and Ryon, 1945).

The clinical toxicity is low: no deleterious effects have been noted with doses of 1 to 6 Gm. in adults, even intravenously, or with plasma concentrations of 5 to 22 mg. per 100 cc. (Abt and Farmer, 1938).

The human requirements of ascorbic acid are not definitely known, nor how they vary for different ages, conditions and individuals. The criteria range from what is indispensable for normal capillary resistance, to saturation of the tissues by various test methods. According to the present imperfect data, they lie within 8 to 50 mg. daily for infants, 22 to 100 mg. or more for children, and 28 to 100 or more for adults. Adequate incomes, but with little margin of safety, are probably 20 mg. for infants, 40 for children and 60 for adults (S. L. Smith, 1938).

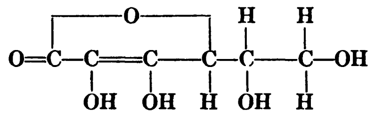
For adults, Pijoan and Lozner, 1944, found 18 to 25 mg. per day the minimum income to protect against scurvy; 80 to 100 mg. per day produced saturation, as judged by urinary excretion. The adequate intake should be somewhere between these figures. Daily excretion of less than 10 to 15 mg. indicates deficiency (Abbasy *et al.*, 1935). Ralli *et al.*, 1939, found that 100 to 135 mg. daily are required to maintain the plasma concentration above 1 mg. per 100 cc. Schultzer, 1937, found 40 mg. intravenously curative for moderate *scurvy. For infants,* 30 to 50 mg. daily are generally curative for acute scurvy, and 10 to 15 mg. prevent active symptoms. Breastfed infants obtain 40 to 50 mg. (Selleg and King, 1936); but cows' milk averages only about half that of the human (Whitnah and Riddell, 1936), and feeding formulas may furnish only a tenth as much as breast milk (Wachholder, 1936), so that they should be supplemented by orange juice.

Natural Sources of Ascorbic Acid.—Fresh orange or lemon juice contains about 1000 international units or 50 mg. of ascorbic acid per 100 cc. (60 to 70 mg., Harris and Ray, 1935). They have been used for prevention of scurvy in the ships of the East India Company since 1601 (E. L. Kennaway, 1942). Lime juice is effective when fresh, but deteriorates more rapidly than lemon juice (Hassan and Basili, 1932). A half pint of orange juice (240 cc.) contains more than 100 mg., and is therefore more than enough for all requirements from infancy to old age; but these may be supplied more cheaply by vegetables; in low-cost diets by potatoes, properly prepared.

Among the richest natural sources of ascorbic acid are the citrous fruits, tomatoes, green peppers and raw cabbage. The commercial canned orange juices contain 30 to 56 mg. per 100 cc.; tomato juice 13 to 29; pineapple juice 10 to 18 (E. M. Bailey, 1938). Rose hips are forty times more potent than orange juice. Half a hip meets the daily requirement of an adult (C. F. Wang, 1944). Practically none is contained in dry cereals and legumes, or in butter, eggs and cheese, and not much in milk. A tabulation of the ascorbic acid content of foods is given in the review of Bessey, 1938. A food should not be considered as a valuable source of ascorbic acid unless it provides a daily intake of at least 12.5 mg. (250 units) of ascorbic acid. The ascorbic acid of vegetables is oxidized and destroyed in ordinary drying, but may be preserved by rapid desiccation and exclusion of air (A. F. Hess, 1921).

Ascorbic acid as such is administered as tablets of 0.01 Gm. (equivalent to 20 or 30 cc. of orange juice). This is the daily protective dose for infants; for treatment, 0.06 Gm.; for adults, 0.05 to 0.1 Gm. per day. For parenteral administration, hypodermic or intravenous, in gastro-intestinal disturbance, 50 to 150 mg. per day, freshly neutralized by half its weight of sodium bicarbonate to prevent acid-necrosis and hemolysis (B. H. Fisher and Leake, 1934; H. H. Anderson and Leake, 1935).

***Ascorbic acid,** U.S.P., is prepared commercially from vegetable sources, from adrenal glands, and by synthesis.



It occurs as white, odorless crystalline powder, freely sol. in water, sol. in alc., insol. in ether. Stable if pure, but in impure preparations and in many natural products it oxidizes on exposure to light and air, and is incompatible with iron and other oxidizing agents. These also destroy it in fruit juices. *Dose,* 10 to 100 mg. per day; 50 mg. (¾ grain) daily, U.S.P.

Ascorbic Acid Tablets, U.S.P., are usually available as 25, 50 and 100 mg. *Sodium Ascorbate Injection,* U.S.P., in water for injection. The usual sizes are equivalent to 0.1 Gm. of ascorbic acid in 2 cc., 0.5 Gm. in 2 cc., in 5 cc., and in 10 cc., and 1 Gm. in 5 cc.

Vitamin P.—Szent-Györgyi *et al.,* 1936, found that paprika and lemon juice contain another substance than ascorbic acid, apparently a flavone which controls hemorrhage in various conditions, especially in clinical cases of increased capillary vulnerability (Scarborough, 1939; Kugelmass, 1940), in retinal hemorrhage and apoplexy. Isolated as crystals from lemon juice, the substance was named *citrin* and was found to consist of a mixture to two related flavone glucosides, *hesperidin* and *eriodictyol* (Szent-Györgyi, 1938). It is apparently identical with *rutin,* present in many plants, prepared from tobacco and most economically from buckwheat leaves (J. F. Couch *et al.,* 1946). This appears sometimes to decrease capillary fragility (J. Q. Griffith *et al.,* 1944), but further experience is needed (Report of Council on Pharmacy and Chemistry, J.A.M.A., *131:*743, 1946; R. L. Shanno, 1946).

VITAMIN A: THE ANTIXEROPHTHALMIC VITAMIN AND CAROTENE

Deficiency of this vitamin causes night-blindness, and excessive keratinization of surface epithelium, manifested especially as xerophthalmia. It is a primary alcohol of the benzene series ($C_{20}H_{29}OH$), consisting essentially of a half molecule of beta carotene ($C_{40}H_{56}$). It is not synthesized in animals, but is formed in the liver by the cleavage of certain vegetable carotenes and cryptoxanthin, which have been termed "provitamin A." These form its chief source in food. It may be administered as carotene, but is generally given as vitamin A, in the form of cod liver oil or other fish liver oils, or concentrates consisting of their nonsaponifiable lipoid fractions. These are more readily absorbed than is carotene, and they also contain the anti-rachitic vitamin D. Vitamin A is rather readily destroyed by oxidation, especially if dissolved in warmed fat, but in natural foods it is not materially weakened by ordinary cooking and careful canning (reviews: L. B. Mendel, 1933; Wilbur and Eusterman, 1933).

Other Questionable Therapeutic Uses.—The Council on Pharmacy and Chemistry reports that there is no adequate evidence for the usefulness of vitamin A in protection against colds, in prevention of renal calculi in man, or for treating hyperthyroidism, anemia, degenerative conditions of the nervous system and ulcerative conditions of the skin.

Historical.—About 1913, several American investigators discovered that butter fat contains some ingredient necessary for growth and nutrition, which is lacking in lard. As the chemical composition of the two fats is similar, they assumed some accompanying substance, which they named "fat-soluble vitamin A." They found that its deficiency could be supplied by cod liver oil, egg yolk and many vegetables. It was later shown that plants do not contain the vitamin, but owe their effect to the carotenes and related substances, which do not act as such but are transformed into the vitamin in the liver. The connection between carotene and vitamin A activity of vegetable foods was noted in the earlier investigations, but the experiments with feeding isolated carotene were then unsuccessful, because it had been oxidized in the isolation. Later work (von Euler, T. Moore) showed that pure carotene is highly effective, 0.003 mg. per day sufficing for the vitamin A need of rats. Carotene had been discovered in carrots by Wackenroder in 1831, and isolated as crystals by Willstaetter, 1910. Its constitution has been determined chiefly by P. Karrer, 1933, who also prepared the vitamin A synthetically. Biologically active preparations have been synthesized by N. A. Milas, 1946. The natural vitamin A was isolated and crystallized from fish oils by H. N. Holmes and Corbet, 1937.

Carotene (Provitamin A) is a lipoid-soluble yellow pigment (lipochrome) occurring in many plants. It is a strongly unsaturated aromatic terpene, $C_{40}H_{56}$. The crystals are readily oxidized with total loss of physiologic activity, so that special precautions are necessary for their conservation. It occurs in three isomeric modifications, the optically inactive betacarotene being by far the most widely distributed. It is twice as effective biologically as the dextrorotatory alpha-carotene, or the gamma form. The more important sources of carotene are carrots, sweet potatoes and yellow corn. Some of the carotene exists as such in animals, especially in eggs, butter, corpus luteum, blood, fat and most of the viscera, probably derived entirely from the food (von Euler, von Euler and Hellstrom, 1928). It is increased by the administration of carotene. Some 30 or more related *carotenoids* are known, but only one of these, cryptoxanthin, is converted into vitamin A in life, in addition to the three carotenes. *Lycopene,* the red pigment of ripe tomatoes, is isomeric with carotene. *Xanthophyls,* the yellow lipochromes of leaves, also belong to the carotenoid pigments, but are not converted into vitamin A. Carotene, lycopene, xanthophyl and capsanthene (red pepper pigment) occur in human fat to the total of 1 to 3.5 mg. per Kg. (Zechmeister and Tuzson, 1935). Many species of bacteria synthesize carotenoids and some carotene itself (Baumann, Steenbock and Ingraham, 1933). The function of carotene in plants is not known. It usually appears concurrent with active growth and closely associated with chlorophyll. Etiolated shoots contain little, suggesting that light is concerned, but once formed it does not disappear on yellowing in the dark (Bessey and Wolbach, 1938). The yellow color of *egg yolk* is due to carotenoid pigments, chiefly xanthophyls, ingested in the food (L. S. Palmer, 1915).

Conversion.—Vertebrate animals are not known to synthesize any carotenoid; but probably all can convert certain carotenoids into vitamin A, although the efficiency of the conversion may differ with the species. The transformation occurs in the liver, presumably by an enzyme. It is stored almost exclusively in the liver fat (Thomas Moore, 1931; Oleatt and McCann, 1931). Vitamin A is formed only from the four carotenoids which possess the beta-ionone ring structure. The conversion has also been accomplished by chemical means (review, L. S. Palmer, 1938). Hypodermic or intravenous injection of carotene does not secure nearly so good utilization as does oral administration, but if it is solubilized by polyethylene gluccol ("Tween 80") it is effectively converted into vitamin A on intramuscular injection (R. M. Tomarelli *et al.*, 1946). In rats, parenteral administration of carotene secures its deposition in the liver, but this is not effective against vitamin A deficiency, as is oral administration, suggesting that the transformation of carotene into vitamin A does not occur in the liver, but in the intestinal epithelium (E. L. Sexton, 1946). Further investigation is needed.

Absorption.—Vitamin A is readily absorbed from the intestinal tract under normal conditions; the absorption of carotene is variable and much more subject to interference with adverse conditions. Fats and oils promote, and mineral oils greatly impede, the absorption. Emulsion of liquid petrolatum interferes with carotene absorption quite as much as does the unemulsified (A. C. Curtis and Balmer, 1939). Absence of bile prevents the absorption of carotene, and probably interferes with that of the vitamin (Drummond *et al.*, 1935; Dutcher *et al.*, 1934; R. W. Jackson, 1934; Altschul, 1935; Greaves and Schmidt, 1935). Vitamin A is also absorbed fairly readily from hypodermic injection. Vitamin A itself is utilized equally well with injection and with oral administration. A colloidal suspension of carotene may be injected by vein, but its therapeutic efficiency is only 1 to 10 per cent of the oral administration, since the colloidal vitamin deposits largely in organs other than the liver (Lease *et al.*, 1942).

In a patient with a fistula of the thoracic duct, Drummond *et al.*, 1935, recovered from the chyle about 90 per cent of the vitamin A that was administered by mouth. It was present chiefly as esters of fatty acids. The absorption of carotene amounted only to 5 or 10 per cent. Virtanen and Kreula, 1941, report that only 3 per cent of the carotene of cooked carrots, and 2 per cent of ground raw carrots, are absorbed in man. Van Eekelen *et al.*, 1938, found that two healthy adults absorbed only 1 to 6 per cent of the carotene of carrots and spinach, but up to 60 per cent of isolated carotene dissolved in oil. Vitamin A in oil solution is absorbed most effectively from the upper and middle thirds of the small intestines. The absorption is promoted by physostigmine, retarded by atropine (Popper and Volk, 1944; Inglefinger *et al.*, 1943). Bile salts render carotene diffusible through colloidal membranes (von Euler and Klussmann, 1933).

Storage.—The vitamin A store normally varies with the carotene content of the diet. About 95 per cent of the total body store is in the liver, the remainder chiefly in the kidneys, lungs and suprarenals. The Kupffer cells appear primarily concerned in its storage and destruction (Domagk and Dobeneck, 1933; Young and Weld, 1935). It can be recognized microscopically by its fluorescence, as droplets in the epithelium and Kupffer cells of the liver, and in the adrenal cortex (Popper, 1940). When it is absent from the liver, it is also absent from the other organs. The store is small in the newborn, and increases rapidly through the milk nutrition, more rapidly by augmenting the vitamin A in the diet of the mother (Baumann, Riising and Steenbock, 1934). In adult animals, the liver store begins to increase within a few hours after administration of a large dose of the vitamin A; over 70 per cent of the quantity administered may be thus stored. A rat can store enough from one feeding of cod liver oil or carotene to supply its requirements for more than two months (McCoord and Luce-Clausen, 1934; C. A. Baumann *et al.*, 1934).

The vitamin A concentration of human livers averages 200 international units (0.1 mg.) per Gm. of moist tissue for adults, 130 units for children, 17 units for infants; but there is considerable variation in normal livers (J. B. Ellison and Moore, 1937). Fish livers run much higher, suggesting that fishes can synthesize the vitamin without carotene.

The vitamin A concentration of the blood depends on the dietary income. Severe hepatic damage is also associated with low A concentrations in the blood, correlating with the clinical course and function tests (D. Adlersberg *et al.*, 1945). Consistently low blood levels indicate depletion. It does not correlate well with biophotometric data (Steininger *et al.*, 1939). S. W. Clausen *et al.*, 1940, report that administration of *ethyl alcohol* to dogs mobilizes vitamin A from the tissues so as to increase its concentration in the blood; and L. B. Pett, 1940, claims improved biophotometric readings on the day after ingestion of alcohol.

Carotene is normally converted into vitamin A and stored in the liver, especially in the Kupffer cells, except a small amount which circulates in the blood and tissues. The blood serum contains normally about 0.11 mg. per 100 cc., and this is doubled or tripled in diabetes, presumably owing to diminished convertive capacity of the liver (Ralli *et al.*, 1936; Stueck *et al.*, 1937). At these upper levels, the carotene causes a visible yellow tint of the palms of the hands, soles of the feet and subconjunctival fat. Such carotenemia may also be produced by excessive medicinal administration of carotene. The conversion into vitamin A is also inhibited by other hepatic disease.

The phenomena of vitamin A deficiency are manifested clinically by night blindness and by excessive keratinization of the epithelium of the skin and mucous membranes, especially of the cornea and conjunctiva (xerophthalmia or keratomalacia), and also of the tongue, mouth, respiratory and urinogenital tract. This favors penetration of bacteria and therefore infection. There is no convincing evidence that systemic resistance to infection is lowered, except in the extreme degrees of deficiency which may be produced experimentally in animals and lead to malnutrition, inhibition of growth and cachexia. The phenomena are similar in man and all mammals and birds that have been studied. The requirement of vitamin A is small, at most a few milligrams daily for the largest mammals. Recovery from deficiency is rapid when the vitamin is again supplied, so that the change in the epithelium may be demonstrated in a few days (review, Bessey and Wolbach, 1938). The curative action is not local but systemic, for if oil with vitamin A is dropped on the conjunctiva of one eye of a keratomalacious rat, both eyes improve at the same rate (de Rötth, 1940). Ordinary diets evidently contain enough vitamin A to prevent conspicuous deficiency phenomena, although the margin is probably not wide. Close observation of low income groups almost always shows conjunctival xerosis, which yields to vitamin A administration (H. D. Kruse, 1941). Subnormal nocturnal vision, with minor degrees of "night blindness," responding promptly (within two weeks) to the administration of vitamin A, is apparently common in children, and the prophylactic administration of vitamin A, along with the D of cod liver oil, is advised by pediatrists. The more severe deficiency phenomena are seen especially when the income and absorption of the vitamin are decreased by prolonged gastro-intestinal disturbance. Toxic effects from overdosage of vitamin A have not been well studied, but are not likely to occur with reasonable doses, since the storage would provide a wide margin of safety. Severe deficiency may lower resistance to bacterial infection, but moderate deficiency does not appear to do so, and additional vitamin A certainly does not diminish susceptibility, for instance, to colds.

Historical.—Xerophthalmia and its treatment by liver diet are described in the Egyptian papyrus of Ebers, about 1500 B.C. (Hess, 1929). Administration of liver in night blindness (hemeralopia) was advocated by Hippocrates. Magendie in 1820 described the occurrence of perforating corneal ulcers in dogs fed exclusively on sugar, olive oil or butter. Similar eye affections were recorded by Livingstone, 1857, when his expedition was on limited rations. Nutritional keratomalacia was described by Bitôt, 1863 (Wilbur and Eusterman, 1934). Eye disease was occasionally observed by Osborne and Mendel, 1913, in their rats on restricted diets.

Experimental Deficiency Phenomena.—Young animals respond promptly to vitamin A deficiency by arrested growth and xerophthalmia. In young *rats*, this may develop in two or three weeks. Deficient bone formation is manifested by delayed dentition and by rickets. In adults, the results may not be notable for several months, partly because adults usually start with a larger store of the vitamin, and partly because they do not need the vitamin for growth. The body weight gradually decreases, the fur roughens, the rats are less agile, the movements become incoordinated, the feet rough and scaly, the animals are untidy, the eyes less protruding, the voice is hoarse or suppressed. Xerophthalmia sets in about this point, with the eyes glued shut, then purulent. Rhinitis with profuse discharge is frequent. Priapism occurs in a third of the males. The resistance to infections is lowered, and the intestinal bacteria invade the blood stream. Anemia does not appear to be a feature, but the blood platelets are said to be diminished (Cramer, 1925; Falconer, 1925). Female rats with insufficient vitamin A or carotene have only few offspring, and these are born with malformation defects of the eyes (Warkany and Schraffenberger, 1944). Sterility develops; indeed, a diet adequate for growth may not contain enough for reproduction (reviews, Mendel, 1933; Orten *et al.*, 1938).

Monkeys on a diet deficient in "A" lose appetite and weight, develop fatal colitis and die, without xerophthalmia, sinusitis or tongue abscess. Epithelial changes may be observed in the respiratory and genito-urinary tract. The animals probably succumb to the gastroenteritis before the keratomalacia has time to become prominent (E. B. Tilden and Miller, 1930; Turner and Loeb, 1932).

Night blindness (nutritional nyctalopia or hemeralopia) is one of the earliest clinical symptoms of vitamin A deficiency. It has no relation to xerophthalmia, the external eye disease following more severe deficiency, but depends on interference with the regeneration of visual purple which is essential to vision under faint illumination. It is most marked after exposure to strong light, which depletes the purple. This type of night blindness responds promptly to vitamin A therapy, improvement being demonstrable two hours after treatment starts. Cases that do not respond are due to congenital defects or other causes (review, Wilbur and Eusterman, 1934).

Incidence.—Nutritional night blindness is not uncommon in the Orient and in some European states. Few if any pronounced cases have been authenticated in the United States, but mild degrees are demonstrable by photometric reading in 26 to 75 per cent of children, the percentage being inverse to the presumptive carotene income of each group; all are promptly cured by the daily administration of 3000 units of vitamin A (Jeans *et al.*, 1937). Jeghers, 1937, found the condition in 10 to 50 per cent of adults, correctable by 30,000 units of vitamin A or carotene daily for three weeks. The minimal daily income for prevention is 4000 units. Experimental reduction to 200 units produced low photometric readings in six days, and subjective symptoms in five weeks. Failures to pass the night glare test of the Army are generally due to vitamin A deficiency and are remedied by its administration (Hutter and Dieter, 1943). Different individuals vary greatly in their response to vitamin A deprivation, to the administration of a single large dose, and to the resumption of a normal diet (Mandelbaum and Hecht, 1940).

Visual purple of the retinal cones is a carotenoid protein, formed continuously in the retina by the union of vitamin A and a carotenoid, "retinene," with protein. Light changes the visual purple to visual yellow. Darkness reverses the reaction and restores the purple and vitamin A (G. Wald, 1935). Fridericia and Hohn, 1925, showed that vitamin A deficiency delays or hinders regeneration of visual purple; Yudkin *et al.*, 1931, found that the retina contains a large amount of the vitamin. This appears also to be a precursor of the visual violet of the rods, for their threshold changes like those of the cones, for instance in alcoholic hepatic cirrhosis (C. Haig *et al.*, 1938).

Keratinization.—Aside from the chemical relation of vitamin A to visual purple, its primary action is on epithelial structures, its deficiency resulting in keratinizing metaplasia, with atrophy of the normal epithelium and substitution of a stratified keratinized epithelium, identical in all locations, and arising from proliferation of the basal cells, which undermine and replace the original epithelium. The swelling leads to occlusion of duct structures and retention cysts, which have been mistaken for abscesses. In man, the trachea and bronchi are the earliest and most common location of the metaplasia; then comes the renal pelvis. Xerophthalmia is rather late. Tooth formation especially of the enamel is deranged. Repair occurs rapidly when the deficiency is met, unless tissue was destroyed (Wolbach and Bessey, 1942).

The changes involve all epithelia that are replaced from basal cells; not those that divide directly, as in the liver, kidney tubules, gastric and intestinal mucosae. The effects begin with atrophy of the epithelium, reparative proliferation of the basal cells, development of the new cells into stratified keratinized epithelium. In *recovery*, the keratinized cells are shed, and the new cells formed in the stratum germinativum differentiate into the new epithelium characteristic for the location (Wolbach and Bessey).—The effect of vitamin A deficiency appears somewhat analogous to the action of estrogenic hormone on the *vaginal epithelium*. This cornification is the basis of the Evans and Bishop, 1922, test for vitamin A. It is possible, however, that the effect is partly indirect, through the ovary (C. A. Baumann and Steenbock, 1932). Vitamin A deficiency also interferes with fertilization and implantation of the ovum. *Xerophthalmia* (*keratomalacia*), keratinization of the epithelium of the cornea and conjunctiva, is a relatively late manifestation, and therefore is rarely seen in man in the United States; but it is a characteristic feature of the more severe deficiency in rats and other animals. It begins with dryness of the cornea and proceeds rapidly to irritation, suppuration and perforating ulcer of the cornea. Young animals develop xerophthalmia more rapidly (V. S. Nelson and Lamb, 1920; clinical, Pillat, 1929; Mendel, 1931). *Keratoconus* succeeds the acute xerophthalmia in rats. The shape of the cornea is restored in a few weeks by administering vitamin A, but corneal nebulae and myopia persist (J. R. Mutch and Richards, 1939). *Skin changes* are among the earliest manifestations and include dry skin, and papules from follicular hyperkeratosis, with lowered resistance to minor skin infections (MacKay, 1934; Jeghers, 1937). In rats, the *tongue* is involved early, beginning with the sublingual glands. *Dental changes* are striking in the incisor teeth of rats and guinea pigs and have also been observed in the toothgerm of a human infant (P. E. Boyle, 1933). They consist of atrophy and keratinization of the enamel organ and disappearance of the odontoblasts. These regenerate from connective tissue cells when the deficiency is supplied. The changes are radically different from those of scurvy (Wolbach and Howe, 1933). The endochondrial formation of bone is retarded, but this may be partly a result of inanition (review, Wolbach and Bessey, 1942).

Urinary Calculi.—In rats and guinea pigs, prolonged severe deficiency of vitamin A is apt to induce calcareous deposits and calculi of the urinary system from the tubules to the bladder, chiefly around large plaques of desquamated epithelial cells (Steiner *et al.*, 1939). Alkalinization of the urine favors the deposition. The bladder calculi were reported to disintegrate when the vitamin is administered. It is doubtful whether vitamin A deficiency has any relation to urinary calculi in man. Such relation is not supported by the dietary history of the patients, keratinization of the urinary tract is unusual (Kayser), and therapeutic results are not at all convincing. However, urinary calculism has become rare in children since the modern emphasis on dietary vitamins (references, H. L. Kretschmer and Brown, 1939).

Degeneration of the myelin sheath of peripheral nerves, especially the sciatic, and of scattered tracts in the spinal cord begins several days before other signs of deficiency appear in rats and increases to death, with muscular weakness, incoordination, and finally paralysis of the hind legs. Its progress can be arrested by supplying the deficiency (E. Mellanby, 1929, 1931; Satterfield and Sutton, 1935; Zimmerman and Cowgill, 1936). Disproportionate growth of the bone and nervous system may lead to mechanical damage and result in paralysis and nerve degeneration. *Testicular epithelium* undergoes atrophy analogous to other epithelial changes (review, Wolbach and Bessey, 1942).

Resistance to Infection.—If a vitamin A deficiency is so extreme as to produce keratinization, this furnishes less protection against bacterial invasion. There is no evidence, however, that susceptibility is increased in the milder grades of deficiency, and increase of vitamin A above the ordinary certainly does not increase resistance. Its characterization as "anti-infective vitamin" is misleading.

The critical control experiments of G. S. Shibley and Spies, 1934, show that the incidence of *respiratory infections* was not altered by the administration of vitamin A for over a year to normal adults on ordinary diets. Sutherland, 1934, found that the administration of cod liver oil concentrate during six months had no significant effect on infections of control groups of school children. J. M. Lewis and Barenberg, 1938, found essentially the same incidence of infection in a group of children kept for six to eight months on a fourth of the normal A income as in another group with four to eight times the normal income. The livers of children dying of acute infectious diseases generally have a considerable store of vitamin A. *Severe deficiency* lowers the resistance of rats to intraperitoneal injection of virulent bacteria (Boynton and Bradford, 1931). Evidence that marked deficiency may lower resistance in man has also been reported (C. E. Bloch, 1931). Lack of both A and D vitamins does not impair the production of antibodies (Wakeman, 1923). *Growth* is retarded by deficiency of vitamin A, but the effect is analogous to that of deficiency in any other essential food constituent and not specific (Mendel, 1933). Administration of the vitamin beyond the normal income does not increase the growth or nutritional state of infants (Sutherland, 1934; J. M. Lewis and Barenberg, 1938). It has no striking effect on *blood formation*. *Thyroxin* and vitamin A appear to be mutually antagonistic: Abelin *et al.*, 1926, reported that diets rich in cod liver oil or egg yolk decrease the toxic effects of thyroid feeding in rats; von Euler and Klussmann, 1932, reported similar results with carotene, and Eufinger and Gottlieb, 1933, claimed that vitamin A counteracts the effect of thyroxin on the metamorphosis of tadpoles. There is no convincing evidence, however, that vitamin A administration diminishes clinical hyperthyroidism. Conversely, Farold and Peters, 1933, found that thyroxin counteracts toxic overdosage of vitamin A. Abelin, 1933, found that thyroxin administration to guinea pigs decreases the vitamin A content of their livers; and Farold and Heidemann, 1933, reported that excision of the thyroid from goats interferes with the conversion of carotene into vitamin A (review, Clausen, 1938). The *oxygen consumption* of rats is not appreciably affected by vitamin A deficiency (Törnblom, 1935).

Toxic effects from overdosage of vitamin A have not been well studied, but they are not likely to occur with any reasonable dosage, since the storage provides a wide margin of safety.

Decalcification and multiple fractures of bones, cachexia, catarrh of the mucosae, damage to the kidneys and other viscera, trophic changes of the skin, and exophthalmos have been obtained by feeding excessive doses of fish oil to animals (Harris and Moore; von Drigalski and Laubmann, 1933). Profuse internal and subcutaneous hemorrhages occur by *decrease of prothrombin*. Administration of vitamin K prevents this, but not the other effects (Light *et al.*, 1944). Large amounts of *pure crystallized vitamin A* produce the bone changes but no significant visceral alterations (Collazo and Rodriguez, 1933). Noetzel, 1939, administering 40,000 units or more to rats, reports marked changes in the liver (fatty degeneration of the Kupffer cells, decrease of glycogen, loss of weight), and fat deposition in the reticulo-endothelial cells of the spleen, bone marrow and kidneys. Cod liver oil, 0.7 Gm. per Kg. daily, shortened the life span of rabbits, and 2 Gm. per Kg. had this effect on calves (W. A. Turner *et al.*, 1936).

Carotene appears to be practically nontoxic on intraperitoneal or intradermic injection (H. G. Wells and Hedenburg, 1916; J. T. Lewis and Reti, 1935); but upon intraperitoneal injection, pure carotene reacts as a foreign body, and produces granulomatous lesions (C. L. Conner, 1928). No carotene appeared in the blood or urine after large amounts. Intravenous injection produced no effect on rabbits. In man, especially in diabetes, excessive administration of carotene produces a yellow coloration of the skin, but no harmful effects. Extractives are said to be more toxic than pure carotene to rats (Lewis and Reti). Hess and Myers described a clinical carotenemia which occurred in infants receiving carrots in the diet, but on discontinuance of the carrots in the affected cases, pigmentation slowly disappeared, Pigmentation did not occur in the absence of carrots (review, R. Kuhn, 1933).

Unit and Assay.—The international unit for vitamin A is 0.6 microgram (0.0006 milligram) of beta carotene. This is also the unit of the current U.S.P.

It corresponds approximately to ⅔ of the obsolete unit of the older U.S.P., Sherman and A.D.M.A. The U.S.P. XII assay is made on the growth of young rats depleted of vitamin A by a special diet. It may also be estimated by a vaginal smear test on rats; or spectrographically (review, Munsell, 1938); and by the "*Carr-Price reaction*," a blue color which appears when antimonyl chloride solution is added to a chloroform solution of vitamin A. This gives consistent results when properly made; but carotene also gives the reaction, developing more slowly (Popper and Steigmann, 1943). Vitamin A differs from its precursors by having no absorption band in the visible spectrum, but a rather broad band in the ultraviolet. In common with all substances of the polyene structure, it gives *color reactions* with numerous agents, including antimonyl trichloride (blue violet for vitamin A, intense blue for carotene).

The daily requirements of vitamin A for man are not accurately known. They appear to increase with the weight and to decrease with age, and the two factors balance each other fairly closely so that there is probably not much difference in the gross needs of infants and adults. The League of Nations Committee advises 6000 to 8000 units for the diet of infants, and at least 5000 for pregnant and nursing women. A daily income of 10,000 units is certainly more than adequate (review, Booker, 1938).

In animals the level of vitamin A or carotene intake required for growth and for prevention of night blindness amounts to 25 to 30 units per Kg. of body weight per day, for all vertebrates (Guilbert *et al.*, 1937). This would come to 1750 to 2100 units for a 70 Kg. man; 3000 units would allow a 50 per cent margin for incomplete absorption. *Cockroaches* do not need vitamin A in their diet throughout their life cycle (Bowers and McKay, 1940).

Dietary Income.—Normal *infants* grow on 24 ounces of breast milk, representing somewhat less than 1500 units. The average diet for children in American hospitals contains 5000 to 6000 units per day and seems to be adequate. The addition of a quart of milk or a teaspoon of cod liver oil would raise this by 1000 or 3000 units. (Skimmed milk is of course poor in vitamin A.) A study of adult dietaries of American families for 1935 to 1936 (H. K. Stiebeling) averaged 2200 to 6200 units in cities, 3000 to 7200 units on farms, varying with the geographical location and the food cost. This would indicate that many of the lower income group have little or no margin. Jeghers, 1937, concluded that clinical deficiency symptoms appear in *adults* when the dietary income is below 4000 units.

Food Sources.—The foods which may serve as sources of vitamin A, directly or through carotene, may be classed as: *Excellent:* Butter (about 20 units per gram), cream, milk, carrots (raw), cod liver oil, eggs (yolk), spinach and water cress. *Good:* Cooked vegetables, bran, whole wheat, cheese, liver, fruits and tomatoes.

Milk contains both vitamin A and carotene; either may predominate. The vitamin A level, 1000 to 2000 units per quart, tends to be constant for a given animal, regardless of the income. Human milk contains more than cows' milk. *Egg yolk* contains vitamin A, not carotene. Its color is due to zeaxanthin and xanthophyl, which are not convertible into vitamin A. *Spinach* is reported to be considerably more effective against night blindness in very young children than the corresponding units of cod liver oil (Friderichsen and Edmund, 1937). Varying results have been obtained on adults. H. E. C. Wilson, 1937, found the absorption of carotene from *raw carrots* or cooked spinach to be 80 to 90 per cent if the diet contains moderate amounts of fat, 50 per cent if it does not.

Administration.—Routine administration of vitamin A is advisable for children under two years, especially those on artificial food; otherwise it need only be administered when real deficiency is present. It is usually given as cod liver oil or its concentrates, which also furnishes antirachitic vitamin. It is even more abundant in the liver oil of other marine fishes of the percomorph group. Halibut liver oil may be a hundred times more potent than that of the cod liver; and others may be still richer, but the potency varies greatly in different catches (Bills *et al.*, 1935).

Carotene has no advantage over vitamin A, and its variable absorption and greater instability make it less desirable. It may be administered in oil, adjusting the dosage to correspond to vitamin A units.

If the income of vitamin A is adequate, neither the absence nor the addition of carotene produces any demonstrable effects. It is, therefore, possible to obtain normal growth, maturity and reproduction in the absence of carotene (Palmer and Kimpster, 1919). If vitamin A is deficient, substitution of carotene in sufficient dosage (0.003 mg. per day for rats) corrects the deficiency completely, as concerns growth and fertility (Steenbock *et al.*, 1921; T. Moore, 1930).

Deterioration and Incompatibilities.—Vitamin A is destroyed by direct sunlight, by heating in the presence of air, and by rancidity (A. D. Holmes and Pigott, 1926); but if these are avoided, oily solutions are fairly stable and the use of artificial stabilizers, such as hydroquinone, is not necessary or advisable (J.A.M.A., 1937, *109:* 1454). Iron salts and other oxidizing agents hasten the destruction. Porous adsorbents are also destructive (H. N. Holmes and Corbet, 1939). The nature of the oil diluent has considerable effect on the absorption (Dyer *et al.*, 1934). *Mineral oil* interferes with the absorption of vitamin A, especially of carotene, but not of vitamin D (R. W. Jackson, 1934; Dutcher, Harris *et al.*, 1934).

Clinical Dosage.—The prophylactic dose of cod liver oil is 2 teaspoons per day, regardless of age. This corresponds to about 6500 units of vitamin A, with the minimal content of the U.S.P., 850 units per Gm. It also furnishes a minimum of about 650 units of vitamin D, on the basis of 85 units per Gm. In starting treatment of an actual deficiency, a larger quantity, up to 4 teaspoonfuls of cod liver oil, would be administered temporarily to speed the cure. Doses larger than 15 cc. daily are not more effective (Spence). The dosage of other fish oils, concentrates and carotene would be adjusted to furnish equivalent units.

Parenteral Administration.—Vitamins A and D are absorbed and effectively utilized if concentrates are injected hypodermically or intraperitoneally; but cod liver oil should not be so injected, as its fat is poorly absorbed and causes local irritation (Koene and Mendel, 1929). Davson, 1936, described marked phagocytosis, fibroblasts and young capillaries.

COD LIVER OIL AND OTHER FISH LIVER OILS

The oils expressed from the liver of cod and other marine fishes are convenient means of administering simultaneously vitamins A and D. These oils are the most concentrated natural source of A vitamin, which was discussed in detail in the preceding section. Vitamin D will be discussed with viosterol (see Index). Both vitamins are contained in the unsaponifiable lipoid; they are, however, quite distinct. Active concentrates are marketed. The official cod liver oil contains at least six hundred times as much A as does butter, so that a teaspoonful of the cod liver oil would represent 6 pounds of butter or 9 gallons of milk. Liver oils that are far richer still in A, without corresponding increase of D, are obtained from halibut and other marine fishes. These make it possible to reduce the dose of oil, the D vitamin being added by blending with other fish oils, or as viosterol. The exclusive milk diet of infants is apt to be deficient in both vitamins A and D; cod liver oil is therefore probably a better prophylactic against rickets than viosterol alone. Later, when the diet is more varied, the artificial introduction of vitamin A is less important, and viosterol is preferred, partly because it avoids the fishy taste. Cod liver oil has been advertised to protect against infections, because deficiency of vitamin A lowers resistance. There is no critical evidence, however, that increase of A income beyond that in normal diet has any additional protective value. The oil may be of some use if the diet is restricted in amount or variety, for instance, with the capricious appetite of phthisical patients.

Historical.—F. W. Headland ("Actions of Medicines," 1856) states that "it appears that the oil from livers of fishes was used as a remedy among the Hindoos and Burmese in very ancient times." "Since time immemorial" cod liver oil was collected for use in the arts, especially in the manufacture of leather; and like everything else, it was used as a folk medicine in the maritime districts of the countries bordering on the North Sea and the Baltic, where the fish are caught, in Scandinavia, Germany, Holland and Great Britain; especially against chronic rheumatism and rickets (which was described by Francis Glisson in 1650), scrofula and phthisis. The first known mention of its professional use is by T. Percival, 1771, from the Manchester Infirmary, where it was introduced, probably about 1766, against chronic rheumatism. Little attention was paid to it until the publication of a paper by Schenck, 1822, in Hufeland's Journal, on its use especially in sciatica and lumbago. This was followed by numerous commendatory papers, extending to scrofula and tuberculosis; including the "Treatise on Oleum Jecoris Aselli" (1841) of J. Hughes Bennett of Edinburgh. The first definite record of its professional use in rickets is in a paper by Schuette, 1824 (Headland, 1856, l. c.; George B. Wood's Therapeutics, 1856; A. Hess, "Rickets," etc., 1929; R. A. Guy, 1923). The use of the oil had periodic waves of popularity and distrust, until the efficacy in rickets was definitely confirmed by roentgenology, and animal experimentation permitted proper control. Before the recognition of vitamins, the activity of cod liver oil was attributed either to its caloric value as an easily emulsified (Buchheim, 1874) and assimilated, unsaturated fat (Motram, 1915), or to traces of compounds of iodine, phosphorus, amine bases (Gautier and Mourgues, 1888).

Assay.—Medicinal cod liver oil is now assayed on rats for both vitamins. Color tests have been proposed, but they are not altogether reliable (Y. Takada, 1927; E. R. Norris and Danielson, 1929).

Administration.—Buchheim remarked in his "Arzneimittellehre" (1853 to 1856): "Because of the nauseating odor, it is well to hold the nose while taking the dose." Infants do not object to it; with older children and adults, the dislike usually decreases on continued use. Some prefer emulsions, or peppermint or wintergreen flavor; others do not care for perfume with fish. The taste is best minimized by careful preparation of the oil and by cooling on ice; or by administering the concentrate in capsules. The oil is perhaps best given as a single dose, once a day, before breakfast; or two hours after a meal. It may produce eructations and diarrhea, especially in the summer; and indigestion and fever are contraindications. Both the A and the D effects can be secured by parenteral administration (Koene and Mendel, 1929), but this is not convenient.

The administration as prophylactic against rickets should begin two to four weeks after birth, increase in dosage to the fourth month, and be continued to two years. A daily dosage of 625 D units probably suffices for adequate protection. This is furnished by three daily doses of 2.5 cc. of cod liver oil of minimal U.S.P. and B.P. potency. Negro infants probably require somewhat more, 4 to 5 teaspoonfuls per day. Large doses may be given temporarily in starting the treatment.

Local Action on Wounds.—The application of cod liver oil dressings or ointment (33 per cent in petrolatum) to burns, ulcers and infected superficial wounds was reported to accelerate healing and decrease infection; but better controlled observations failed to show superiority over other ointments (review, Council on Pharmacy and Chemistry, J.A.M.A., 1943, *121*:759).

Beneficial results were reported by H. Lücke, 1933 and 1935; von Drigalski, 1934; and J. P. Steel, 1935. Lauber and Rocholl, 1935, attributed the effect to the epithelial action of vitamin A. Löhr and Unger, 1937, report that not only A, but also the D and the glycerides of the unsaturated fatty acids of cod liver oil accelerate healing, and that vitamin concentrates above those in cod liver oil retard healing. H. R. Getz, 1938, reported cure of *tuberculous ulcers* in guinea pigs by the topical application of cod liver oil; but that the potency is not parallel to the vitamin A content, although it resides in the nonsaponifiable fraction. *Sodium Morrhuate* has been tried *hypodermically*, like sodium gynocardate, against *tuberculosis and leprosy*. B. Rogers, 1918, claimed good results, but these lack adequate confirmation.

Sodium Morrhuate as Sclerosing Agent.—Intravenous injection of $\frac{1}{2}$ to 1 cc. of five per cent solution of this cod liver oil soap causes sclerosis, thrombosis and obliteration of the veins, which is utilized in the treatment of varicose veins.

PREPARATIONS.—***Cod Liver Oil,** U.S.P. (Oleum Morrhuae; Ol. Jecoris Aselli), is the partially destearinated fixed oil from fresh livers of Gadus Morrhua and other species of the family Gadidae. It occurs as a pale yellow thin oil, having a peculiar fishy but not rancid odor, and a bland fishy taste. It thickens on exposure to air. The U.S.P. requires that each Gm. of oil shall contain at least 850 units of vitamin A and 85 units of vitamin D. Most medicinal brands contain at least 100 units of D, chiefly 7-dehydrocholesterol, the same as is formed in the skin. When materially more than the U.S.P. requirements is contained in cod liver oil it should be given in proportionately lower dose. One "United States Pharmacopoeia Unit of Vitamin A" is equal, in growth-promoting and antiophthalmic activities for the rat, to one International Unit of Vit. A as defined and adopted by the Conference of Vitamin Standards of the Permanent Commission on Biological Standardization of the League of Nations in June of 1934; one "United States Pharmacopoeia Unit of Vitamin D" is equal, in antirachitic potency for the rat, to one International Unit of Vit. D (see Index under Vitamin D). The average *dose* for infants and adults, 8 cc., 2 drachms, corresponds to 6800 units of A and 680 units of D. Flavoring may be added. *Cod Liver Oil Emulsion,* U.S.P. (Emuls. Olei Morrhuae), contains 50 per cent oil and is sweetened and flavored acacia emulsion. Dose, infants and adults, 15 cc., 4 drachms. *Burbot liver oil* is similar to cod liver oil. It is adjusted to a potency of not less than 4480 units of vitamin A and not less than 640 units of vitamin D, per gram (N.N.R.).

Cod Liver Oil Concentrate (Liquid), N.N.R., is a concentrate of the nonsaponifiable fraction of cod liver oil, dissolved in a neutral oil. The vitamin A potency must be between 50,000 and 65,000 units, the D potency between 5000 and 6500 units per gram. It may be dispensed in *capsules* of not less than 5000 A and 500 D units, and in *tablets* of not less than 3120 A and 312 D units. The prophylactic *dose* is 6 to 12 drops, or 1 to 2 capsules, or 2 to 6 tablets daily.

Oleovitamin A, U.S.P. (Natural Vitamin A in Oil), is fish liver oil or concentrate diluted with vegetable oil so that each gram contains about 50,000 units of vitamin A and not more than 1000 units of vitamin D. Average prophylactic *dose* for adults or infants, 0.1 cc. daily. It may be dispensed as *Oleovitamin A Capsules,* U.S.P., containing either 5000 or 25,000 units per capsule.

Oleovitamin A and D, U.S.P., is adjusted to contain, per gram, about 925 units of vitamin A and 92.5 units of D. It may be flavored. The average *dose* for adults and infants is 8 cc. daily.

Concentrated Oleovitamin A and D, U.S.P., an oily liquid, contains, per gram, about 57,500 units of A and 11,500 of D vitamin. The average prophylactic *dose* for adults and infants is 0.1 cc. daily. It is available as *Capsules,* U.S.P., each containing 5000 units of A and 1000 of D.

***Halibut Liver Oil,** U.S.P. (Oleum Hypoglossi), is a fixed oil obtained from halibut livers. It contains, per gram, not less than 60,000 units of vitamin A and not less than 600 units of vitamin D. Flavors may be added. The average prophylactic *dose* for infants and adults is 0.1 cc. daily. It may be dispensed as *Capsules,* U.S.P., each containing 5000 or 25,000 units of vitamin A.

Percomorph Liver Oil, N.N.R., is a blend of oils obtained from various percomorph fishes, assayed and adjusted to a potency of not less than 60,000 units of vitamin A and 8500 units of vitamin D per gram.

Shark Liver Oil is adjusted to 16,500 units of vitamin A and 40 units of D per gram. It is marketed as capsules of 0.3 cc., containing not less than 5000 units of vitamin A.

Carotene in Oil is a solution in cottonseed oil, assayed to a potency of 7500 vitamin A units (4.5 mg. of beta carotene) per Gm.

THE VITAMIN B COMPLEX

Plants of all kinds contain water-soluble vitamins which promote nutrition. Diets that are deficient in these lead to arrest of growth, loss of appetite and weight, anemia, nervous and circulatory disturbances, skin lesions and progressive inanition which terminates in death by starvation. The phenomena are promptly corrected when food or watery extracts containing these vitamins are added to the diet. These events are complex resultants of the deficiency of a number of soluble substances, which generally occur together and which were therefore originally considered as one and designated as "*water-soluble growth vitamin*" or "*vitamin B,*" and now as the *vitamin B complex*. They are especially abundant in yeast, liver and bran (rice polishings); and these are the usual source of the complex. They are apparently essential constituents of enzyme systems that control certain oxidation-reduction reactions of carbohydrate metabolism in living cells. The antineuritic factor was the first to be differentiated as "B_1," from the growth factors "B_2" or "G" or "P-P" (pellagra preventive), and the complex has been resolved by special solvents and adsorbents into ten or more entities, characterized by specific deficiency symptoms, nutritional, dermal or paralytic, often confined to definite species of animals, rats, chicks or pigeons. Only three of these are definitely known to be connected with deficiency symptoms in man: thiamine with the polyneuritis of beriberi; nicotinic acid amide with the skin and nervous changes of pellagra; and riboflavin with certain dermatoses. These have been isolated, identified and synthesized, as has also a fourth principle, "B_6" or "Pyridoxine," which is connected with dermatosis in rats and apparently with some clinical conditions. Others are known only by their effects.

The B-complex vitamins *protect the liver* against functional and structural impairment by a variety of toxic agents. Deficiency of B-complex income impairs the liver so that it fails to inactivate estrogenic hormones, resulting in menorrhagia (M. S. Biskind and Biskind, 1942). Vitamin B complex *increases the inactivation of estrogen* (not of testosterone), and good results have been reported from its administration in menorrhagia and other forms of menstrual hyperactivity (M. S. Biskind *et al.*, 1944).

Vitamin Complex Preparations.—Since these vitamins occur together, deficiencies generally include more or less of the whole "complex," so that it may be advantageous to administer preparations containing all the potent components.

The *average American diet* before the enrichment of bread contained less of the B-complex vitamins than is now considered desirable: Thiamine, 0.8 mg. per 2500 calories instead of 1.6 as recommended; riboflavin, 1.4 mg. per day instead of 2.2 mg.; nicotinic acid, 11 mg. per 2500 calories instead of 15 mg. (editorial, J.A.M.A., 1945, *127*:160).

The following *groups of preparations* are recognized in N.N.R.:

(1) Mixtures of pure thiamine, 1 mg.; riboflavin, 2 mg.; nicotinic acid, 10 mg.; in daily dose or simple multiples.

(2) Dried brewers' yeast, assayed as such, or (3) fortified with thiamine and riboflavin; or (4) as a concentrate; or (5) fortified with riboflavin and nicotinic acid.

(6) A concentrate from liver with not less than 0.25 mg. of riboflavin per Gm.

(7) A concentrate from rice polishings, fortified with riboflavin and nicotinic acid.

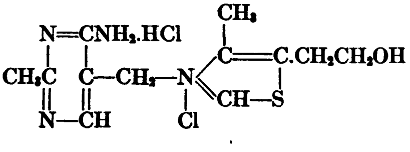
U.S.P. Vitamin Complex Preparations include *Yeast* (see Index) and *Rice polishings* (Perpolitiones Oryzae), *U.S.P.;* Rice Bran, Tiki Tiki.—*Extract of Rice Polishings,* U.S.P., is assayed to contain 20 units of thiamine per cubic centimeter. It is a viscous liquid. Average dose, 8 cc.

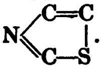
THIAMINE

This is the "antineuritic vitamin" or "B_1," deficiency of which results in polyneuritis and the clinical disease beriberi. Its chemical constitution has been established as a basic compound of pyrimidine and thiazole, and it is manufactured synthetically and marketed as the hydrochloride. It occurs in probably all animals and plants, both free and as thiamine pyrophosphate or cocarboxylase, which functions in living cells as co-enzyme in intermediate carbohydrate metabolism reactions, some oxidizing, some decarboxylizing. It plays a conspicuous role in the growth of all living organisms, from the lowest to the highest plants and animals. The normal human income is 1 to 2 mg. per day, and this probably does not leave a wide margin. It is apparently nontoxic in considerably larger doses. Its administration prevents and relieves the deficiency phenomena. Its usefulness has been demonstrated in beriberi, in some anorexias of dietary origin; and to insure optimal growth of infants and children. It may have a considerably wider scope, but this has not been established. (The subject is discussed in detail in the book of R. R. Williams and T. D. Spies, "Vitamin B_1 (thiamin) and Its Use in Medicine"; MacMillan, 1938.)

Historical.—Beriberi, an endemic peripheral polyneuritis with nutritional disturbances, spread rapidly in the Orient about the middle of the nineteenth century, when hulled rice was introduced. Admiral Takaki in 1884 demonstrated that the disease in the Japanese navy was due to this rice diet. In 1897 Christian Eijkmann, at that time stationed in Java, chanced to notice that chickens fed on the cooked rice discarded at the hospital developed polyneuritis. He recognized its similarity to beriberi, and found that it could be averted and promptly cured by feeding rice hulls or extracts from these. Yeast extracts are also effective. Casimir Funk, 1911, obtained crystals from rice hulls; but when purified, these proved to be nicotinic acid (Drummond and Funk, 1914), which is ineffective against the deficiency neuritis. Highly active concentrates were obtained by special adsorbents and differential solvents (A. Seidell, 1926), and the crystallized active principle was finally isolated by Jansen and Donath, 1926, who named it "aneurin"; and on a practical scale, as the hydrochloride, by R. R. Williams, Waterman and Keresztesy, 1934. The structural formula was determined and its synthesis accomplished by Williams and Kline, 1926, and Williams proposed the name thiamine.

Chemistry.—Thiamine hydrochloride has the *structural formula:*



This structure is chemically unique. The ring to the left is pyrimidine, to the right is derived from thiazole, . The latter is otherwise unknown in nature, and thiamine is the only vitamin known to contain sulfur. The position of the alkyl in the pyrimidine is also peculiar; and the N forms a quaternary base. The dry substance is stable in air, but neutral and alkaline solutions are rapidly destroyed, especially on heating, by hydrolytic cleavage into the constituent pyrimidine and thiazole ring. Acid solutions can be boiled over half an hour. The activity is rapidly destroyed by sulfite. The oxidation product, *thiochrome*, probably a dehydroderivative (Bergel *et al.*, 1935), is not antineuritic (Kuhn and Vetter, 1935). The oxidation is not reversible. The loss of activity in the cooking of foods is quite small, perhaps by the formation of stable esters with pyrophosphoric acid; but it disappears gradually from stored foods. The activity remains when yeast is autolyzed at 35° C. for 24 hours (Cooper, 1914).

Thiamine pyrophosphate, cocarboxylase, is widely distributed in nature, in animals chiefly in the liver and kidneys, along with thiamine. They are probably in dynamic equilibrium, with the pyrophosphate generally predominant (M. A. Lipschitz *et al.*, 1938).

Synthesis in Vivo.—Animals, including insects, can not synthesize thiamine even from its cleavage products, and must therefore obtain it fully formed from plants, directly or indirectly. It is manufactured by intestinal bacteria.

Plants synthesize it chiefly in the leaves. It is stored in the seeds for the needs of the embryo. Roots and lower plants require an extraneous supply, but can often utilize the intermediates, thiazole and pyrimidine, for the synthesis. Although yeast appears to be able to synthesize thiamine, its content generally depends on the amount of preformed thiamine in the cultural medium; it is therefore richer if grown on grain than on molasses media. Isolated roots also require nicotinic acid, pyridoxine and other vitamins which are normally synthesized in the leaves of intact plants (W. J. Robbins and Bartley, 1937).

Food Sources.—Thiamine occurs in all natural foods, in concentrations of 0.1 to 4 micrograms per Gm.

In plants, the average of 1 to 2 micrograms (about ½ unit) is exceeded only by seeds, especially the hulls and embryos, and by yeast grown in thiamine-rich media. "Wheat germ" or embryo, a by-product in the mills of the flour, contains it in much higher concentration than the endosperm. In animals, the liver, heart and kidney contain about 3 micrograms. Pork muscle is outstanding with 10 micrograms (all ratios are per Gm. of fresh food) (review, Munsell, 1938).

Fate and Storage.—Thiamine is readily absorbed from the normal digestive tract, but persistent diarrhea may lead to deficiency. The urinary excretion is small, the fecal still smaller. The greater part is temporarily stored in the various tissues, especially the liver and muscles, which contain more than half of the total store; but the storage capacity is limited, the thiamine is rapidly destroyed and any excess is merely wasted. If the income stops, deficiency symptoms appear in a week with pigeons (Pilcher and Sollmann, 1925), in ten days with rats, in three to four weeks with dogs (review, Cowgill, 1938). The organs are not devoid of thiamine when polyneuritis sets in. The liver loses ⅔ of its store in a week, then more slowly. The brain content is normally rather low, but is held more tenaciously than that of other organs.

The urinary excretion of thiamine in man amounts normally to 0.03 to 0.2 mg. per day, equivalent to 5 to 35 per cent of the amount ingested. The excretion after subarachnoid injection is less rapid than with oral, intramuscular or intravenous injection. A fifth to a fourth of the orally ingested thiamine may escape absorption and be eliminated by the feces (Siclounoff).

Human sweat excretes about 5 per cent of the normal intake of thiamine, about 3 per cent each of the riboflavin and pantothenic acid, and about 0.5 per cent of nicotinic acid (Cornbleet *et al.*, 1943).

The deficiency phenomena produced experimentally from synthetic diets approach those of *clinical beriberi* resulting from diets restricted too exclusively to hulled rice or white wheat flour. After about ninety days of such diets, the symptoms begin with fatigue, numbness and stiffness, tenderness and tingling of the legs, followed by their more or less complete paralysis, due to degeneration of the myelin sheaths of the peripheral nerves. Other situations may also become involved; for instance, the larynx. Parallel with these is loss of appetite and inanition, with or without edema (the "wet" and "dry" forms). Cardiac hypertrophy develops in man, and results in sudden death by acute cardiac dilatation. Animals generally die of inanition (review, Vedder, 1937).

Experimental thiamine deficiency in man, induced by eighty-six days of diet containing less than 0.15 mg. per day, but adequate in other respects, results in some of the neurotic symptoms of beriberi, but lacks the edema and cardiac dilatation. Clinical beriberi probably involves also other deficiencies (R. D. Williams, Mason *et al.,* 1940).

Vitamin B Deficiency on Work Output.—Decreasing the B-complex income of trained human subjects to about a third of the recommended daily requirement is reported to result in diminished work output by producing easy fatigue, muscular pain, irritability, anorexia and lowered pyruvic acid level of the blood. These effects disappear in a few days if the dietary deficiency is met (Barborka *et al.,* 1943). In rats, also, dietary thiamine deficiency produces rapid decrease of work performance as measured by swimming; with restoration on replacing the thiamine; but administration of thiamine to nondeficient animals does not improve their normal performance (Kniazuk and Molitar, 1944).

Rice Disease in Birds.—The phenomena, which have been studied especially in pigeons and chickens, are essentially identical with those in man. Pigeons fed exclusively on hulled ("polished") rice promptly lose their appetite, with almost parallel loss of weight, anemia, lassitude, weakness, diminished heat production, fall of body temperature and depressed respiration. Death occurs in about three to five weeks, when the body weight has fallen by 35 to 55 per cent, as in ordinary starvation. The nutritional disturbances are the most constant feature of the rice disease. Polyneuritis, characterized by muscular paralysis, occurs in less than half of the birds, after two to five weeks, usually in three. It is possible that it would develop also in others if they lived long enough (Eijkman, 1890 to 1897; Casimir Funk, 1911 to 1913). The malnutrition is also quite variable. The previous diet plays a rather minor part; if it was rich in vitamin, the malnutrition is delayed by about a week, corresponding to the limit of vitamin storage; if the diet was so poor in vitamin that the animals start with subnormal weight, the starvation proceeds more rapidly (Pilcher and Sollmann, 1925). Young animals are more susceptible than the full grown; with young rats, growth is arrested in two to three weeks. Pregnant and diseased animals are also more susceptible. McCarrison claims that partial vitamin B deficiency produces loss of appetite, diarrhea, atrophy of the lymphoid tissue of the intestines, especially of Peyer's patches, and sterility. The inanition is accompanied by *degenerative changes in the viscera* (McCarrison, 1919), essentially identical with those of simple inanition. This includes atrophy of the intestinal villi, leading to bacteremia. The *blood changes* are also identical with those of simple inanition; the total corpuscles decrease somewhat more than the body weight, and there is also hydremic plethora (Barlow and Biskind, 1928). These changes usually precede the degenerative lesions of the peripheral nerves and later of the spinal cord.

Beriberi in Mammals.—Typical beriberi polyneuritis has been produced in cats and dogs by an exclusive diet of lean meat, heated for three hours at 120° C. with sodium carbonate solution. Different animals require different periods to develop the disease. The pathology and the response to treatment are the same as for beriberi (Voegtlin and Lake, 1919). The condition, however, is complicated by other deficiencies. Rats on a hulled rice diet died from inanition, with relatively little anemia and no polyneuritis; the condition is completely relieved by the same agents as beriberi (Whitehead, 1930). Increased spontaneous activity and hyperexcitability are early indications of deficiency in rats (Bloomfield and Tainter, 1943). The acute deficiency phenomena in cats include impairment of reflexes involving synaptic centers in the midbrain (G. M. Everett, 1944).

Nervous phenomena begin with fatty degeneration of the myelin sheath of the peripheral nerve fibers, and then involve the axis cylinder, similar to the changes of nerve section, presumably by inability of the neurons to utilize carbohydrates (Wolbach and Bessey, 1942). There are also degenerative changes in the ganglion cells throughout the central nervous system. "Multiple neuropathy" describes the condition more accurately than "multiple neuritis," as the process is degenerative and not inflammatory. Similar changes are found in chronic alcoholism and lead poisoning, diphtheria toxin and starvation (Wechsler, 1938). They appear rather late in thiamine deficiency, and are probably secondary to the nutritional disturbance, but the point of attack appears to be different from that of simple starvation, for the latter is not affected by the administration of thiamine, which relieves the functional phenomena of thiamine deficiency in five or six hours (review, Wolbach, 1937). *Thujone convulsions* are not significantly influenced by thiamine deficiency or administration (Molitar and Sampson, 1937). *Striated Muscle* is not affected directly by thiamine; concentrations above 1:3,000,000 depress acetylcholine contracture. It increases potassium contracture (Torda and Wolff, 1944). It inhibits the muscle response to nicotine; this is not counteracted by physostigmine (Unna and Pick, 1944). It contracts physostigminized *leech* muscle (Byer and Harpuder, 1940).

Diminished food consumption and absorption is a basic phenomenon of thiamine deficiency, and many of the deficiency symptoms occur in control animals which receive similarly limited quantites of food with adequate thiamine (Cowgill, 1938). The marked *anorexia* of thiamine deficiency is the result of incapacity to digest, propel and assimilate food, and forced feeding results merely in stagnation of undigested food in the alimentary tract (Cowgill *et al.,* 1925). Symptomatic treatment of the digestive derangements by laxatives (Barlow and Biskind, 1928) or histamine (Danysz-Michel and Koskowski, 1922) is partly effective while atropine, epinephrine and pilocarpine accelerate the starvation (Arloing and Dufourt, 1923). Adsorbents (kaolin, charcoal, etc.) diminish the effect of thiamine (Masserli, 1922) by decreasing its absorption. Thiamine deficiency inhibits the *normal secretory and motor functions* of the stomach and probably of the intestinal tract (Uhlmann, 1918; McCarrison). *Excised intestinal segments* from such animals also show decreased motility and resistance (B. A. Plummer, 1927), and are less sensitive to acetylcholine. The addition of thiamine restores the susceptibility, although it does not increase the response of normal intestines (Abderhalden and Abderhalden, 1938). (Thiamine inhibits choline esterase, but only with concentrations much higher than those that occur in animals; Glick and Antopol, 1939.) The movements of normal excised intestines are not affected by the addition of thiamine, 1:1000 (Hecht and Weeve, 1937; Molitor and Sampson, 1936); nor has administration of thiamine any material effect on the appetite or the digestive functions of intact normal animals (Cowgill and Mendel, 1921). It sensitizes rat intestine to acetylcholine, but does not sensitize many of the other parasympathetic innervations (Byer and Harpuder, 1940). In 1:10,000 it inhibits the actions of nicotine on rabbits' isolated intestines, but has no effect on the response to ortho- and parasympathetic drugs (Unna and Pick, 1944). The failure of thiamine to affect gastro-intestinal functions directly indicates that the digestive depression is the result rather than the cause of the nutritional disturbance. The *intestinal bacterial flora* is modified and increased by the digestive stasis. The resistance of the intestines is lowered (W. B. Rose, 1928) and the blood is invaded with the ordinary intestinal bacteria (McCarrison, 1919; Barlow, 1927 to 1929). It has not been proved whether these have any special relation to the symptoms. The anemia, at least, appears to be chiefly a part of the general consumption of the tissues in the inanition (Moore and Barlow, 1931). The anemia changes present similarities to those of pernicious anemia (Dhar, 1925; Gildea *et al.*, 1930). A specific beriberi bacillus was claimed by Matsumura and Kakinuma, 1929. Thiamine deficiency shortens the incubation period of *rat leprosy* (Badger, Masumaga and Wolf, 1940).

Growth is checked or arrested by the malnutrition of thiamine deficiency, and is promoted when this is met by thiamine administration; but excess income does not increase growth beyond the normal rate or degree.

Metabolism.—The need for thiamine is greater if metabolism is increased, as in *thyroid poisoning*, and conversely, thiamine has a protective action against the toxic effects of thyroxin (Sure and Buchanan, 1913; Drill and Sherwood, 1938). *High carbohydrate consumption* increases the thiamine need (Funk, 1914) and introduction of carbohydrates into the crop of thiamine-deficient birds is toxic.

Thiamine administration diminishes the metabolic response to *thyroid* (R. D. Williams and Kendall, 1943). The thiamine level of the blood is generally subnormal in thyrotoxic patients (R. H. Williams, Egana *et al.*, 1943).

Fatty diet tends to spare thiamine and to cure spastic polyneuritis in rats, glyceryl caprylate being the most effective (H. M. Evans *et al.*, 1934). Conversely, thiamine appears to be necessary for the deposition of fat (Best and McHenry, 1937). Rats with deficient thiamine income show marked craving for fatty soaps. Deficiency of A, B or D vitamins decreases the rate of intestinal absorption of fat, probably in consequence of the impaired nutrition (review, A. C. Frazer, 1940). *Glycogen storage and the blood sugar level* are often deranged in thiamine deficiency, but not always, and the disturbance could be secondary to the inanition (Reader and Drummond, 1926). Abderhalden and Wertheimer, 1933, reported rise of blood sugar and of liver glycogen. Enlargement of the islands of Langerhans has been reported (Wolbach, 1937). *Changes in tissue respiration* had been described: Hess, 1921; Abderhalden, 1922; Mattill, 1923; C. J. Farmer and Redenbaugh, 1925; but Fleming, 1923, did not find any significant peculiarities in the metabolism of beriberi patients.

Co-Enzyme Function in Intermediate Carbohydrate Metabolism.—The pyrophosphoric ester of thiamine has been identified as *cocarboxylase* (1-4), the prothetic group for enzymes concerned with the oxidation, carboxylation, descarboxylation, dismutation and condensation of pyruvic acid (R. A. Peters, 1936; R. R. Williams, 1938). The latter is an obligatory intermediate in the normal carbohydrate breakdown, and probably in the interconversion of proteins, fats and carbohydrates. High pyruvic acid content of the blood is clinical evidence of thiamine deficiency.

Ingestion of dextrose by normal individuals increases the blood pyruvate. In thiamine deficiency the pyruvate curve rises higher and persists longer (Bueding *et al.*, 1941).

The thiamine of yeast is probably entirely in the form of its pyrophosphate ester; in rice hulls it is probably free. Both forms are antineuritic, but it is possible that the biologic utilization of thiamine is preceded by its conversion into the pyrophosphate. Hexose diphosphate, adenosine triphosphate and phosphopyruvic acid have been suggested as phosphate donors. On bacteria it has been shown that thiamine must be phosphorylated before becoming part of the pyruvic oxidizing system (Barron and Lyman, 1938). Iodoacetic acid inhibits the enzymatic synthesis, fluoride does not. Riboflavin forms a similar system. The wide distribution of thiamine, ascorbic acid, nicotinic amide and riboflavin indicates that they are essential for most if not all living cells, presumably as links of enzyme reactions that effect cellular metabolism. *Co-enzymes* are generally nucleotides connected with nucleoproteins and the cell nucleus. Many vitamins and some of the hormones of animals act as "*nutrilites*" to promote the growth of plants and lower organisms.

The chief metabolic reactions in which the cooperation of thiamine has been definitely demonstrated are the decarboxylization of pyruvic acid, and indirectly the oxidation of lactic acid, in nervous tissue, yeast and bacteria.

The involvement of the nervous system in thiamine deficiency is presumably connected with its dependence on the oxidation of carbohydrates (review, Wolbach and Bessey, 1942). Deficiency of nicotinic acid, riboflavin, pantothenic acid and pyrodoxine also results in degenerative changes of the central nervous system; but A, C, D and E vitamins affect nervous structures only indirectly (H. E. Himwich, 1943).

Brain tissue removed from thiamine-deficient pigeons shows an abnormally low oxygen uptake when suspended in Ringer-phosphate, in the presence of dextrose, lactate or pyruvate. The addition of thiamine to the suspension restores the normal oxygen consumption, apparently by the removal of the pyruvate which is present in increased amount in the thiamine-deficient brains. This is designated as the "*catatorulin effect.*" With brain, the pyrophosphoric ester has only a tenth of the potency of free thiamine. The addition of thiamine has no effect on suspensions of normal brain (Passmore, Peters and Sinclair, 1933; review, Quastel, 1939). *Methylglyoxal* occurs in considerable amount in the blood in thiamine deficiency (Arakawa, 1930; Uga, 1935). *Glutathione* is diminished, especially in the muscles. *Yeast fermentation* requires the presence of the thiamine pyrophosphoric ester (cocarboxylase), which is contained in the yeast, plus a specific yeast protein, carboxylase, the two together decarboxylizing pyruvic acid into acetaldehyde: $CH_3COCOOH \rightarrow CH_3CHO + CO_2$. Free thiamine does not produce this effect (Lohmann and Schuster). *Plants in general* probably require thiamine for their metabolism, but most are able to synthesize what they need, except some parasitical and saprophytic forms. Some of these can synthesize it if supplied with pyrimidine and thiazole, some with one or the other, and some can not form it even when both these intermediates are supplied. Thiamine or thiazole enables excised tomato roots to grow without tops, in dilutions as high as $1:10_9$ (W. J. Robbins, 1939).

Circulation.—The plasma volume is markedly decreased by the digestive disturbance, and this also results in *anemia. Cardiac hypertrophy* is a prominent feature in clinical beriberi. It is responsible for the dilatation of the right heart, pulmonary edema and congestion of the portal and splanchnic viscera. Its causation is not clear, but it may disappear promptly when thiamine is administered (review, Strauss, 1938).

Deficiency of thiamine, riboflavin and the other components of the vitamin B complex does not produce vasomotor changes in human subjects (G. M. Roth *et al.*, 1943). Thiamine administration is reported to increase the resistance of dogs to hemorrhage *shock* (Govier and Greer, 1941). In rats and pigeons, thiamine deficiency causes *bradycardia*, progressing to heartblock, appearing somewhat earlier than the polyneuritis (Drury. 1930; C. W. Carter, 1930). This constitutes one of the assay methods (Birch and Harris, 1934), but the results are not quantitatively consistent (Munsell, 1938). If there is no thiamine deficiency, its administration has no effect on the heart, nor does a 1:1000 solution affect the excised frog heart (Hecht and Weese; Molitor and Sampson). It does diminish vagus stimulation by acetylcholine (P. Kaiser, 1939). On the other hand, vitamin B augments the action of acetylcholine on denervated muscle of leech, on isolated intestine and on the circulation of cats (Agid *et al.*, 1937; Abderhalden and Abderhalden, 1938). It does not act as antiesterase (B. Minz, 1938).

The toxicity of thiamine is generally low. Rats have been raised on 5 mg. per day for three generations. It has been administered clinically in doses of 500 mg. daily for months, without producing any detectable effect after the deficiency symptoms were met. In other cases, however, ordinary full therapeutic doses, 17 to 40 mg. per day, may produce symptoms similar to thyroid hyperactivity, such as tremors, tachycardia and nervous irritability (C. A. Mills, 1941). *Sensitization* by repeated intravenous injection has been reported, with phenomena similar to serum anaphylaxis, including acute collapse (C. L. Laws, 1941; L. Schiff, 1941). *Sudden death*, with collapse symptoms, has followed intravenous injection of 100 mg. (Reingold and Webb, 1946).

The *lethal dose* for intravenous injection has been determined as 125 mg. per Kg. for mice, 250 for rats, 300 for rabbits and 350 for dogs. Death occurs by failure of respiration, preceded by shock, muscle twitching, clonic spasm, dyspnea. The heart and blood pressure remain good until the respiration fails. The fatal dose with hypodermic injection is about six times, and with oral administration about forty times that by vein. This would make the oral fatal dose for man about a kilogram (Molitor and Sampson, 1936; Hecht and Weese, 1937). Repeated intravenous injections of large doses (100 mg. per Kg.) into rabbits do not produce anaphylactic sensitization, but rather lower the toxicity (T. J. Harey and Flesher, 1946).

Unit and Assay.—The International Unit is 3 micrograms of thiamine hydrochloride, and this is taken as a standard of comparison for foods and pharmaceutical preparations. Other units are obsolete.

Some twenty methods of assay are currently used and advocated, but none seems to be altogether satisfactory. Those based on the prevention and cure of the deficiency polyneuritis deserve preference as being most specific, and the curative dose is the most reliable. The U.S.P. assay is based on the cure of rat polyneuritis induced by a deficient diet. R. R. Williams *et al.*, 1934 and 1935, showed that 0.001 to 0.002 mg. of the pure principle protects pigeons and rats fully against B_1 deficiency. To secure full growth requires a considerably larger dosage than that which suffices to prevent the neuritic changes. Other methods are based on the growth rate and on bradycardia (C. W. Carter, 1930). Chemical methods have not been developed sufficiently and the micro-organisms are not specific (Munsell, 1938).

The minimal requirements are generally estimated as normally 50 to 75 units (0.15 to 0.23 mg.) of thiamine hydrochloride for infants, and 200 to 300 units (0.6 to 0.9 mg.) for adults, daily, by mouth. (R. D. Williams, Mason *et al.*, found 0.95 mg. per day required to prevent marked deficiency symptoms; with further benefit by 2 mg. per day.) The minimal requirement can be expressed more significantly as 0.35 mg. per 1000 calories; 0.6 mg. per 1000 calories gives a liberal margin to offset possible losses in cooking (Melnick, 1944). *The requirements are raised when metabolism is increased.* These *requirements are increased* up to ten times with high carbohydrate consumption (Vorhaus *et al.*, 1935), forced exercise, thyroid administration or hyperthyroidism (Cowgill), and during fever, gestation and lactation. *Ordinary diets* contain 1 to 2 mg. The average American diet contains 0.32 mg. per 1000 calories (Lane *et al.*) and is therefore adequate, but the margin is not wide and the success of vitamin therapy in various clinical conditions indicates that deficiency is more common than was realized. If the thiamine income is adequate (1 mg. per day, or 0.5 mg. per 1000 calories), some is promptly excreted, so that there is no retention. If it is inadequate, the greater part is retained until the normal tissue concentration is reached (Melnick, 1942).

The richest sources in ordinary foods are the bran coat and the embryo of grains and legumes, and lean pork. The content in human milk depends primarily on the quantity ingested by the mother, so that infantile beriberi was common in the rice countries. Modern wheat flour contains only an eleventh as much thiamine as stoneground flour of olden times (G. R. Cowgill, 1939). A. Z. Baker, Wright and Drummond, 1937, estimate that the daily thiamine income of the indigent of London was 600 to 1100 units, almost twice that of the London highest income groups in 1937 (450 to 550 units). *Raw fish diet* destroys thiamine and so tends to produce deficiency (in foxes; R. G. Green *et al.*, 1941).

Dosage.—This should maintain the daily income at least at the normal minimum, 0.35 mg. of thiamine hydrochloride per 1000 calories of food; 1 mg. daily for adults, 0.25 mg. for infants; and preferably raise it to two or three times this quantity. There is no objection to adding this amount to the ordinary diet, but there is no advantage in raising the prophylactic dosage above 3 mg. for adults or 0.5 mg. for infants. In treating deficiency phenomena, however, it is advisable to administer 10, 20 or even 50 mg. daily, until the symptoms are corrected. These higher doses secure much better results in alcoholic neuritis (Goodhart and Jolliffe, 1938).

The treatment of *severe neuritis* may begin with 50 to 100 mg. per day, parenterally, divided into doses of 10 to 20 mg. If no response is obtained in a week, it is useless to continue. If the response is favorable, the administration may be changed to oral (Aring *et al.*, 1939).

Therapeutic Uses.—Administration of thiamine is indicated whenever the income is insufficient, and not otherwise. The outstanding example of its effective use is in the prevention and treatment of beriberi. The degree of deficiency represented by this disease is not likely to occur with American and European dietaries, however, except perhaps in penal institutions and insane asylums; but deficiency sufficient to produce neuritis occurs in the anorexia of alcoholism and forms a part of the picture of delirium tremens and pellagra. The toxic polyneurites of pregnancy, diabetes, gastric disorders and postinfective conditions have also been attributed to thiamine deficiency (Youmans, 1937). Minor deficiencies, manifested by anorexia and malnutrition, and miscellaneous neurites are difficult to diagnose as such except by their history and by the response to thiamine administration. The increased thiamine needs of pregnancy and lactation, hyperthyroidism and fever may justify its prophylactic administration, especially if digestive disturbance hinders the absorption. This may require parenteral administration. All deficiency phenomena respond promptly and completely to the administration of thiamine or preparations of yeast or rice hulls ("tiki tiki") which contain it. The improvement begins in a few days and "cure" is completed in a few weeks, except that regeneration of injured nerves requires longer; and if the degeneration and inanition are too far advanced, the progress is merely delayed and decline proceeds to death (review, Strauss, 1938).

Alcoholic neuritis does not develop, even with large consumption of alcohol, if the diet is adequate. Jolliffe and Joffe, 1935, found that patients with this condition always had gross dietary insufficiency for at least twenty-two days. If no thiamine at all is consumed, about twenty days elapse before the first neuritic symptoms, and the final stages are reached in a few weeks. In partial deficiency, the neuritis may remain stationary for a long time. *Pellagra neuritis* is promptly relieved by intravenous injection of thiamine hydrochloride, but this has no effect on the stomatitis. Nicotinic acid relieves the latter and not the neuritis (T. D. Spies and Aring, 1938). *The acute neuritis of leprosy* is markedly relieved, often in one to three days, by thiamine injection (Badger and Patrick, 1938). Thiamine is *not analgetic* against the severe pain of cancer, neuralgia or spinal cord tumors, even when 100 mg. per day are injected intravenously for ten days (Aring *et al.*, 1939).

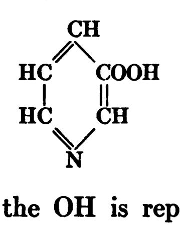
PREPARATIONS: ***Thiamine Hydrochloride, U.S.P.**, thiamine chloride, crystalline vitamin B_1 hydrochloride, aneurine hydrochloride, occurs as white crystalline powder, absorbing water on exposure to air, very soluble in water, the 5 per cent solution having a *p*H of about 3.5. Dose (1 Gm. in about 1 cc.); generally 10 mg. daily. *Thiamine Hydrochloride Tablets*, U.S.P., usually available as 3, 5 and 10 mg. *Thiamine Hydrochloride Injection*, U.S.P., in water for injection; usual sizes, 5, 10 and 50 mg. in 1 cc.; 0.25, 0.5, 1 and 1.5 Gm. in 10 cc.

NICOTINIC ACID (NIACIN)

Most of the phenomena of pellagra in man and an analogous condition, "blacktongue" in dogs, are cured by the administration of nicotinic acid or its amide, and may be considered as due chiefly to deficiency of these dietary factors which form part of the "vitamin B complex," which was designated as "P-P" (pellagra preventive) before the compounds were isolated and identified. Pellagra may also involve additional deficiencies, notably of thiamine and riboflavin, and the symptoms due to these are not removed by nicotinic acid, but only by the addition of the lacking factors. The synonyms "niacin" and "niacinamide" were devised for the lay public to avoid misleading connotations of "nicotinic."

Historical.—The connection between pellagra and restricted diet had long been noted, and Goldberger *et al.*, 1925, and T. D. Spies, 1935, showed that it could be prevented and cured by the administration of yeast extracts containing the "P-P" factor, which also cured the canine "blacktongue," inflammatory and ulcerative changes of the skin and mucous membrane that developed in full grown dogs on restricted diets. Elvehjem *et al.*, 1937, identified nicotinic acid as the effective constituent (review, D. T. Smith and Gower, 1938; Elvehjem, 1939).

Chemistry.—Nicotinic acid is a fairly simple substance, pyridine-3-carboxylic acid:



In the *amide*, the OH is replaced by NH_2, and in coramine by $N(C_2H_5)_2$. Nicotinic acid was originally obtained (1867) by the oxidation of nicotine, and is manufactured synthetically.

Nicotinic acid occurs in rice polishings and yeast (Funk, 1911), and the amide has been isolated from liver. The amide is contained in the *cozymase* which plays an important role in fermentation, glycolysis and respiration. Nicotinic acid inhibits the oxidation of lactic acid in slices of brain; nicotinic amide is much less effective (Z. Baker *et al.*, 1938). Rats do not require nicotinic acid, as they can synthesize it freely (W. J. Dann, 1941), apparently from various simple nitrogen sources, such as amino acids, ammonium and choline (Huff and Perlzweig, 1942). They develop deficiency symptoms if deprived of pyridoxine (B_6), which is chemically somewhat related (S. A. Harris and Folkers, 1939). Rabbits also synthesize nicotinic acid rather freely (Swaminathan, 1942).

Fate.—*The nicotinic amide concentration in the blood* is 0.54 to 0.83 mg. per 100 cc. in normal adult males, 0.52 to 0.74 mg. in females; about 90 per cent of this is in the corpuscles. *The urinary excretion* depends on the concentration in the plasma, not in the whole blood. It amounts normally to 1.7 to 30 mg. per day, free and combined, and about 60 mg. additional as trigonelline after methylation. Oral administration of nicotinic acid results in prompt and marked increase of its urinary excretion, amounting to about 22 per cent of the ingested; about half of this as trigonelline, a third as nicotinuric acid, and an eighth as nicotinic acid or amide. Trigonelline and nicotinic acid, administered as such, are excreted fairly completely and unchanged (Melnick, Robinson and Field, 1940; Sarett *et al.*, 1942). Rats, in contrast to man, dog and rabbit, can destroy trigonelline and nicotinuric acid (Huff and Perlzweig, 1942).

Specificity.—As tested on canine "blacktongue," nicotinic acid, its amide and ethyl nicotinate are about equally potent. Most of the related pyridine derivatives are ineffective when tested against blacktongue of dogs. The only active derivatives are those that can be oxidized or hydrolyzed to nicotinic acid or its amide (Woolley *et al.*, 1938). *Quinolinic acid*, pyridine-2.3-dicarboxylic acid, is strongly antipellagric (Vilter and Spies, 1939).

Clinical Pellagra.—Oral administration of nicotinic acid or amide promptly cures or greatly improves the characteristic phenomenon, including the lesions of the mucous membranes (glossitis, stomatitis, vaginitis, urethritis and proctitis), the early dermal erythema, the mental changes, and the porphyrinuria, even though the diet which produced the disease remains otherwise unaltered; but in this case the lesions return when the nicotinic acid is discontinued (T. D. Spies *et al.*, 1938; D. T. Smith *et al.*, 1937). Nicotinic acid does not cure polyneuritis and cheilosis, which may be associated with pellagra if thiamine and riboflavin are also deficient (Spies and Aring, 1938); nor has nicotinic acid any effect on glossitis and dermatitis or the psychotic states (Cleckley *et al.*, 1939) unless these are due to the specific deficiency. Porphyrinuria, however, is benefited even when it is due to other causes, *f. i.*, lead poisoning (E. S. Gross *et al.*, 1938). Nicotinic acid also relieves specifically the syndrome formerly called "*alcoholic encephalopathy*," characterized by clouding of consciousness, cog-wheel rigidity and uncontrollable grasping and sucking reflex (K. M. Bowman *et al.*, 1940).

Dosage.—The optimal intake of nicotinic acid is not established with certainty, but is probably 15 to 20 mg. per day for adults. The therapeutic dose is up to 500 mg. per day, in ten doses of 50 mg. each, by mouth, or 50 to 80 mg. per day by vein. Oral administration is preferred. Smaller amounts may suffice, or it may be necessary to increase them (Spies *et al.*, 1938). The administration is continued for ten to fifteen days, until the condition is cured. Recurrence is prevented by 100 mg. per week (Elvehjem *et al.*, 1937).

Yeast is effective, but large doses are needed, 60 to 270 Gm. of dried yeast daily (Spies *et al.*, 1937). For *dietary prophylaxis*, milk, lean meat, liver, fish and legumes are considered especially effective (Sebrell, 1937). For *canine blacktongue*, 0.1 mg. of nicotinic acid per Kg. of body weight for ten days is ineffective, 0.2 mg. is slowly effective, 0.5 mg. rapidly, 10 mg. no more rapidly. Coramine requires larger doses, 5 to 10 mg. per Kg., but the results are more lasting (D. S. Smith *et al.*, 1938).

Nitritoid side actions, similar to the effects of histamine, may occur in man with 30 mg. of nicotinic acid and are constant with 100 mg. or higher, orally, or 10 mg. by vein. They are unpleasant but brief and harmless, and do not preclude further administration. Even at their peak, the blood pressure, temperature and respiration are not significantly altered (Spies, Cooper and Blankenhorn, 1938). Susceptibility varies considerably, probably by differences in absorption, for the effects always occur on intravenous injection of 10 mg. (Sebrell and Butler, 1938). They do not occur with nicotinic amide (Bean and Spies, 1940).

The symptoms consist of marked but transient flushing, itching, burning and tingling of the face and upper trunk. The blood pressure, pulse, respiration and temperature are not materially changed. The blood flow is generally increased in the arm, but little in the leg (D. I. Abramson *et al.*, 1940). The cutaneous vasodilatation is produced by nicotinic acid and other compounds containing the free pyridine radical, but not by their amides (Bean and Spies, 1940). Gastro-intestinal motility may be increased. Daily doses of 1 Gm. have been administered without further deleterious effect (Spies *et al.*, 1938; Sebrell and Butler, 1938). The peripheral vasodilatation can not be used for treating peripheral vascular disease, since it is too brief and uncomfortable, and it involves arterial constriction (Popkin, 1939). It often relieves severe idiopathic *headache*, migraine and the headache that follows spinal tapping. The effect appears proportional to the flushing; 100 mg. usually suffice, and produce no untoward effects except uncomfortable heat and brief throbbing (Goldzieher and Popkin, 1946). It has no effect on the course of *experimental hypertension* (H. Goldblatt, Kahn and Lewis, 1942), but is reported to relieve *rheumatoid arthritis*. The flush lasts about an hour after intravenous injection of 200 to 400 cc. of 0.05 per cent in saline. It may be administered orally, three doses of 50 mg. fifteen minutes apart, repeated three times daily, increased to 0.1 or 0.2 Gm. if necessary. No harm followed 5.4 Gm. per day (C. M. Kurtz *et al.*, 1945). There are also reports of marked and lasting relief of *angina pectoris* (F. J. Neuwohl, 1942) and of trigeminal neuralgia (W. E. Adams and Robinson, 1941: 50 to 75 mg. by mouth, two to four times daily). Nicotinic acid increases the acidity and volume of *gastric secretion*, but more slowly than histamine. It was not beneficial to achylia patients (Malaguzzi-Valeri and Paterno, 1939). *Nicotinic acid amide* (but not nicotinic acid) depresses the tonus of the uterus and intestines of guinea pigs, and of the stomach of frogs (L. Liaci, 1940).

The toxicity for animals is low. For rats and mice, hypodermic or oral administration of doses corresponding to 5 or 7.5 Gm. per Kg. are required to kill half of the animals. Dogs may be given 2 Gm. per Kg. orally per day without toxic symptoms. The growth of rats is not retarded by oral administration of 1 Gm. per Kg. daily for forty days, or 200 mg. per Kg. intraperitoneally for twenty-four days. *Intravenous* injection up to 1 Gm. per Kg. had no effect on the blood pressure or electrocardiogram in dogs (K. Unna, 1939; McCrea, 1938).

Addition of 1 per cent of nicotinic acid to a 10 per cent casein diet inhibits the *growth* of rats almost completely, probably because the trigonelline synthesis preempts methyl groups; this may be prevented by adding methionine, not by choline or betaine. The same amount of nicotinic acid has no effect on growth, but produces *fatty liver;* this is prevented by choline, and betaine, as well as by methionine (Handler and Dann, 1942). A *microbiologic assay* for nicotinic acid and nicotinamide, on cultures of Lactobacillus arabinosus, is described in the U.S.P.

PREPARATIONS.—***Nicotinic Acid, U.S.P.,** *Niacin*, occurs as white crystalline powder, sol. in 60 parts of water, freely soluble in alkaline carbonates. Average dose, 25 mg. *Nicotinic Acid Tablets*, U.S.P., usual sizes 25, 50 and 100 mg. *Ampuls* for intravenous injection are usually 1, 2 and 10 mg. per cubic centimeter.

Nicotinamide, U.S.P.; Nicotinic acid amide, niacinamide. White crystalline powder, bitter, odorless. Freely soluble in water (1:1); neutral to litmus. Average dose, oral, 25 mg.; parenteral, 100 mg.—*Tablets of Nicotinamide*, U.S.P., usual sizes 25 and 50 mg.—*Nicotinamide Injection*, in water for injection, usual sizes 100 mg. in 1 cc. and in 2 cc.

RIBOFLAVIN

This substance, also known as lactoflavin, Vitamin G or B_2, occurs widely distributed in living cells, and forms part of an important oxidation-reduction system. It is necessary for the growth of chicks and rats, and its deficiency in rats causes cataract. In man, deficiency phenomena consist in rather minor but specific inflammation and keratosis of the tongue, lips (cheilosis), face and sclera, and vascularization of the cornea. They are usually associated with other B complex deficiencies (review, E. M. Nelson, 1937; W. H. Sebrell, 1937; H. C. Sherman and Lanford, 1937).

Historical.—When the "B_1" of the B complex was destroyed by heating in an autoclave, the residue was found to retain the property of preventing the stunting of rats by certain limited diets, such as oats (Emmet and Luros, 1919; M. I. Smith and Hendrick, 1926). This second growth-promoting factor, which was designated as B_2 or *G*, was then identified with the flavins, a group of nitrogenous water-soluble yellow pigments, or "lyochromes," which occur also in animal fluids and organs, especially in the whey of milk, in eggs and in liver. Several have been isolated pure, as crystals, and these differ rather widely in growth-promoting activity (L. E. Booher, 1933; R. Kuhn, 1933; H. von Euler, Karrer, Adler and Helmberg, 1934; P. György, Kuhn and Wagner-Jauregg, 1934). P. György, 1935, and v. Euler *et al.*, 1935, showed that the synthetic and natural substances are biologically identical. The terms "B_2" and "G" have been applied successively to so many fractions of the complex that their use is confusing.

Chemical and Occurrence.—Riboflavin, dimethyl-ribityl-alloxazin, is a three ring compound with four nitrogens in the rings. It has been synthesized. It is rather heat-stable, especially in acid solution, but is very labile when exposed to light. It is polymeric, one form melting at 281.2°, the other at 293.6° C. (J. A. Means *et al.*, 1943). It is the yellow-green fluorescent pigment of whey, and was known as lactoflavin, ovoflavin and hepatoflavin, according to its source, but these are identical. It is obtainable from many other sources, animal and vegetable. It is formed primarily in green leaves and is most abundant there. The chief dietary sources are milk, cheese, ice cream, meat and fish (reviews, L. E. Booher, 1938; A. G. Hogan, 1938).

Riboflavin is a constituent of the enzyme xanthine oxidase (E. G. Ball, 1939). It occurs as riboflavin (alloxazine nucleotide), the prosthetic group of *flavoprotein*, the "*yellow oxidation enzyme*" of Warburg and Christian, which is present presumably in all living cells, as an essential part of many dehydrogenation systems. It has been suggested that, together with cytochrome, it is concerned in some phase of muscular contraction. A *microbiologic assay* for riboflavin, using Lactobacillus casei, is described in the U.S.P. The activity is confined to a limited range of structural derivatives.

Fate.—Riboflavin is absorbed from the digestive tract (P. György, 1936). It is *stored* in the organs, but the content is not materially increased by raising the income to ten times the normal (R. Kuhn *et al.*, 1935). On the other hand, the store is retained very tenaciously, and is at one-third to one-half of the normal even in rats that die of riboflavin starvation (Vivarico, 1935). When the income is adequate, the excess is excreted in the urine.

A partial supply of riboflavin is furnished by its *synthesis through bacterial action* in the gastro-intestinal tract. This is considerable in ruminants and rats: but man also may continue for months to excrete five to six times the amount of a low riboflavin income (Najjar *et al.*, 1944).

The deficiency syndrome in man is not completely differentiated. The most characteristic feature is cracking and erosion at the corner of the mouth (cheilosis) and roughing of the skin, especially over the nose, which occur in over half of the subjects exposed to the deficiency, and are cured in four to six days by the oral administration of 5 mg. of riboflavin daily (Sebrell and Butler, 1938; Spies *et al.*, 1939; Sydenstricker *et al.*, 1939). The skin changes are like those of pellagra, but riboflavin is not effective against nicotinic deficiency, nor against other nutritional dermatoses of rats and chicks (Sebrell *et al.*, 1937; E. M. Nelson, 1937). The two deficiencies are often concurrent, however, and riboflavin is sometimes a useful adjunct to nicotinic acid (Spies *et al.*, 1939). Its addition to vitamin A is also helpful in resistant cases of night blindness (M. S. Kimble and Gordon, 1939). *Superficial vascularization of the sclera (keratitis rosacea) and of the cornea* is also characteristic of riboflavin deficiency, in man and in animals, and is promptly benefited by riboflavin (Sydenstricker *et al.*, 1940; C. A. Conners *et al.*, 1943). The vascularization of the cornea is presumably a response to interference with its cell respiration (Wolbach and Bessey). *In adult dogs*, riboflavin deficiency causes decrease of appetite and activity, loss of weight, and, after some fifteen to twenty weeks, sudden collapse with bradycardia and arrhythmia, marked fall of temperature, slowed respiration, coma and death. Autopsy shows degenerative changes in the central nervous system and yellow mottling of the liver. Injection of riboflavin causes recovery in three to twenty-four hours, even in advanced cases (Sebrell and Onstott, 1938; Street and Cowgill, 1939; Potter *et al.*, 1942). Intravenous injection of 1 mg. per Kg. prevents anoxic depression of the linguo-maxillary reflex. It also inhibits anoxic depression of the smooth esophageal muscle of frogs (H. F. Hailman, 1944). It promotes hemoglobin regeneration after hemorrhage (György, Robscheidt-Robbins and Whipple, 1938).

Deficiency in rats slowly stunts the growth and lowers the general tone and resistance, with nonspecific dermatosis and loss of hair (von Drigalski, 1935). Diminished skin sensitivity disposes to pediculosis (P. György, 1938). The resistance to endemic murine typhoid is lowered (H. Pinkerton and Bessey, 1939). Keratitis and vascularization of the cornea are frequent. The latter is followed by infiltration with leukocytes, striking changes in the collagen, degeneration of the epithelium and ulceration. Riboflavin administration secures prompt improvement and repair (Bessey and Wolbach, 1939; R. E. Eckardt and Johnson, 1939). *Nutritional cataract* develops in about a tenth of the rats subjected to riboflavin deficiency, starting after about fifty days, as opacity of the fetal nucleus. Once started, it proceeds and involves the other eye, even though riboflavin is administered (P. L. Day *et al.*, 1931, 1938; P. György, 1935; R. E. Eckardt and Johnson, 1939). The normal lens contains two groups of fluorescent substances, flavin and dimethyl alloxazin. In cataract lens the flavin is absent and replaced by a photolytic product, lumiflavin (F. P. Fischer, 1935).

Rats may show partial paralysis of the legs, with degeneration of the myeline sheath and swelling of the axis cylinder in the sciatic and brachial plexus and spinal cord; marked atrophy of the testes and thymus, and structural changes of the thyroid and adrenals in severe cases (Shaw and Phillips, 1941). Riboflavin, like ascorbic acid, antagonizes the rise of temperature by dinitrophenol, thyroxin and external heat, but not that of tetrahydronaphthylamine or protein (H. T. A. Haas, 1939). In growing mice, riboflavin deficiency decreases the *rate of growth* and of ossification, and intensifies the degeneration of the cartilage (B. M. Levy and Silberberg, 1946). In *baby chicks* it produces a characteristic leg disorder and subnormal growth (Bethke *et al.*, 1937).

The *optimal daily intake* of riboflavin is probably about 1 mg. for children, 3 mg. for adults, somewhat higher during pregnancy and lactation. The *therapeutic dose* is 2 to 10 mg. per day, by mouth or, if necessary, by vein. No side effects occur from relatively large doses.

Mice are not injured by a thousand times their normal income (R. Kuhn and Boulanger, 1936). No toxic manifestations occur from long continued daily administration of 10 mg. to rats or 25 mg. to dogs (Unna and Greslin, 1942). On the other hand, restriction of the dietary income of six normal men to 0.31 mg. per 1000 calories for five months caused no deficiency symptoms (Keys *et al.*, 1944).

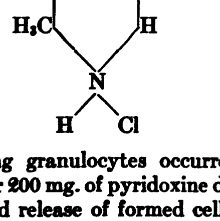
Preparations.—*Riboflavin*, U.S.P. (lactoflavin, vitamin B_2, vitamin G), occurs as clusters of fine orange-yellow needles. It is slightly soluble in water (1:10,000), very sol. in dilute alkalis, sol. in alc., insol. in ordinary lipoid solvents. It is stable toward heat, oxidizing agents and strong mineral acids, but sensitive to alkali. The watery solution has an intense yellow-green fluorescence, which is abolished by acids or alkalis. It deteriorates rapidly if it is exposed to light. Dose, 2 to 10 mg. per day. *Riboflavin Tablets*, U.S.P., 1 and 5 mg. *Riboflavin Injection*, U.S.P., in water for injection, dissolved with nicotinamide, urea or other harmless agents declared on the label. Usual sizes are 0.25 mg. in 1 cc., 1 mg. in 2 cc., 5 mg. in 2 cc.

MINOR COMPONENTS OF THE VITAMIN B COMPLEX

In addition to thiamine, nicotinic acid and riboflavin, which are needed by all organisms, the "complex" of yeast contains other dietary factors essential for some species, but less definitely for man. A *glossary* of the confusing synonyms is given by E. M. Nelson, 1937.

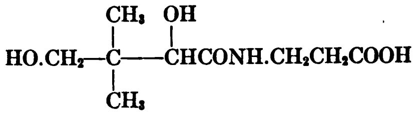
Pyridoxine, *vitamin "B_6" or "H,"* was recognized by P. György, 1934, and synthesized by S. A. Harris and Folkers in 1939; the identity of the synthetic was confirmed biologically by E. J. Reedman *et al.*, 1940. György found that its *deficiency* causes a florid dermatosis in young rats, which can be cured by 0.05 mg. of synthetic pyridoxine hydrochloride per day (Reedman *et al.*, 1940). Presumably other structures are also affected (Wolbach and Bessey, 1942). If the deficiency is prolonged over four months, the rats develop epileptoid attacks (H. Chick, Sadr and Worden, 1940). Chicks do not develop dermatitis, but respond by slow growth, convulsions and other nervous manifestations (Lepkovsky and Kratzer, 1942). Young ducklings show growth failure and severe microcytic anemia; older ducks develop paralyses and convulsions (Hegsted and Rao, 1945). Its toxicity is low; 3 Gm. per Kg. are required hypodermically to produce convulsions and death (K. Unna, 1940; Antopol and Tarlow, 1942).

Deficiency symptoms have not been conclusively demonstrated *in man*, but T. D. Spies, Ladisch and Bean, 1940, report that intravenous injections of 50 mg. of pyridoxine promptly cure residual pellagra symptoms which resist thiamine and riboflavin in some patients. Spies, 1940, believed that its deficiency produces rather ill defined clinical symptoms. He describes marked improvement in postencephalitic Parkinsonian syndrome, with striking relief of the tremor and rigidity in a few minutes after intravenous injection of pyridoxine hydrochloride. Jolliffe *et al.*, 1942, report benefit in persistent adolescent acne; R. S. Willis *et al.*, 1942, in hyperemesis gravidarum. Daily doses of 5 to 250 mg. have been used, usually 5 to 10 mg. of *pyridoxine hydrochloride*. Rapid and significant rise of circulating granulocytes occurred in thiouracil *granulopenia* after 200 mg. of pyridoxine daily; the prompt response indicated release of formed cells (Fishberg and Vorzimmer, 1945). *Roentgen sickness* is reported to be improved by oral administration of pyridoxine hydrochloride (R. J. Reeves, 1946).



Pyridoxal phosphate functions as co-enzyme of amino acid decarboxylase, and of glutamate-aspartate transaminase (H. C. Lichstein *et al.*, 1945).

Pantothenic acid is a growth-stimulating factor which occurs in liver and probably other tissues, in yeast and molds and probably other plants. It is a derivative of beta alanine and has been synthetized by R. J. Williams *et al.*, 1940, and E. T. Stiller *et al.*, 1940.



$$HO.CH_2{-}\underset{CH_3}{\overset{CH_3}{C}}{-}\overset{OH}{C}HCONH.CH_2CH_2COOH$$

Its value in human nutrition has not been clearly demonstrated. Deficiency symptoms in animals include dermatitis, keratitis, adrenal hemorrhage and atrophy, a characteristic depigmentation of hair, and arrest of growth (Woolley *et al.*, 1938; R. J. Williams, 1943; P. György and Poling, 1940; K. Una and Sampson, 1940; L. M. Henderson *et al.*, 1942). Its deficiency inhibits endochondrial ossification in growing mice (B. M. Levy and Silberberg, 1946). The most significant lesion is fatal hemorrhagic necrosis of the adrenal cortex (Wolbach and Bessey, 1942). The intestinal absorption of galactose is decreased by pantothenic deficiency (J. R. Leonards and Free, 1943).

Young *dogs* require about 0.1 mg. of pantothenic acid per Kg. per day. Weaning puppies, after four to six weeks of pantothenic deficient diet, suddenly develop a fatal complex with gastro-intestinal symptoms, prostration, coma and convulsions. Necropsy reveals fatty liver, mottled thymus, hemorrhagic renal degeneration, frequently gastritis, enteritis and intussusception. Intravenous calcium pantothenate and dextrose cures the condition (A. E. Schaefer *et al.*, 1942).

Achromotrichia, graying of the hair, may be produced in rats by deficiency of *paraminobenzoic acid* (Ansbacher). Others have failed to obtain this effect (Unna *et al.*, 1941; L. M. Henderson *et al.*, 1942). Paraminobenzoic acid is not effective against the pantothenic graying, or vice versa. Graying of rat hair resulting from exclusive milk diet is cured by adding Fe, Cu, and Mn to the food (A. H. Free, 1940). Continued ingestion of *phenylthiocarbamide* by black or hooded rats produces graying in four to seven weeks; black hair returns in about ten weeks after discontinuing (C. P. Richter and Clisby, 1942). The natural graying of human hair is not checked by administering pantothenic acid (R. R. Williams, 1940; Kerlan and Herwick, 1943). Brandaleone *et al.*, 1943, report some degree of restoration in exceptional cases under combined treatment with calcium pantothenate, paraminoacetic acid and brewers' yeast.

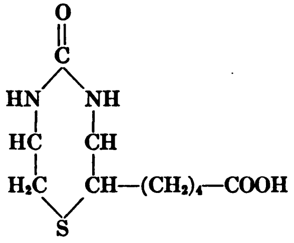
The *toxicity* of pantothenic acid is low; 0.8 to 10 Gm. per Kg. are required to cause death (by respiratory failure). Prolonged feeding with subtoxic doses does not cause any symptoms (K. Unna and Greslin, 1941).

Fate.—In rabbits the blood normally contains 0.05 to 0.07 mg. per 100 cc. It may rise to 9.3 mg. after hypodermic injection of 500 mg. From 50 to 75 per cent of the administered dosage is excreted by the urine within two hours. In man, the blood level is lower, 0.018 to 0.025 mg. per 100 cc., and less is recoverable from the urine (P. B. Pearson, 1941).

For *therapy* in man, Spies *et al.*, 1940, administered 100 mg. of calcium or sodium pantothenate intravenously.

"Folic Acid" (see Index), a "norite eluate of solubilized liver," classed as a B vitamin, plays a role in the production of blood cells.

Biotin, identical with vitamin H and "coenzyme R," has been isolated as a definite compound with its chemical structure (du Vigneaud, 1942) confirmed by synthesis (S. A. Harris *et al.*, 1943; review, K. Hofmann, 1943). It occurs in almost all cells, liver and yeast being especially rich. It is one of the factors in the "bios" of Wildiers (review, R. Hertz, 1946). It is highly potent, promoting the growth of a yeast strain in dilutions of $1:10^{11}$ (Kögl and Tönnis, 1936). It is also essential for the growth of certain bacteria and for strains of the legume-nodule organism Rizobium. Its toxicity is low; the fatal dose for mammals ranges from 0.8 to 10 Gm. per Kg. Death occurs by failure of respiration. Prolonged feeding with subtoxic doses produces no symptoms. It has no effect on the course of experimental hypertension (Kahn and Lewis, 1942).



"*Procarcinogenic*" *Effect.*—Tumor tissue is relatively rich in biotin. Administration of biotin to rats ingesting the dye "butter yellow," dimethyl amino azo benzene, increases the incidence of hepatic carcinoma, while riboflavin and casein confer marked protection (du Vigneaud *et al.*, 1942). Biotin does not increase the growth of transplanted sarcomas in mice.

Biotin is apparently not essential in human nutrition, but information is not adequate.

"Avidin," a specific basic protein constituent of raw egg white, binds biotin stoichiometrically to a nondialyzable compound so that it cannot be absorbed from the intestinal tract, or by yeast. This creates biotin deficiency, manifested in mammals, including man, and birds as "*egg white injury,*" nutritional disorders and especially eczematous dermatitis, curable by administering biotin (Eakin *et al.*, 1940, 1941). Avidin is destroyed by cooking and egg white injury is therefore not likely to occur spontaneously in man; but it may be induced by ingesting 200 Gm. of dehydrated egg white daily for several weeks. The symptoms are similar to those of thiamine deficiency, but are cured by parenteral administration of biotin (Sydenstricker *et al.*, 1942).

"Lysozyme," closely related to, if not identical with, biotin, produces lysis of susceptible bacteria by depolymerizing and hydrolyzing a mucoid of their membrane (K. Meyer, 1944).

Culture-Activating Substance "Bios."—The multiplication of yeasts, infusoria, bacteria and other organisms is more rapid in media on which the organisms have already been grown (within certain limits) than it is in fresh culture media. Wildiers, 1901, and F. B. Robertson ("Chemical Basis of Growth and Senescence," 1923) attributed this to the formation of an autocatalytic agent, "bios." The relation of this factor to the other yeast vitamins has not been worked out. It does not appear to be identified with the B complex (review, F. W. Tanner).

Auxin, a plant hormone (see Index) which stimulates the growth of the stem, the rooting of cuttings and the formation of the fruit from the ovary in higher plants, was isolated by Kögl and Haagen-Smit, 1931. It is part of a respiratory system, effective only when succinic or malic acid is present (Commoner and Thimann, 1941). The same action is possessed by a series of entirely different aromatic acids, indoleacetic, ciscinnamic, nephaleneacetic, phenylacetic, etc., their molar activity being nearly equal (review, F. W. Went, 1943; see Index).

YEAST

The ordinary bakers' and brewers' yeast, "*faex medicinalis,*" consists of the cells of *Saccharomyces cerevisiae,* filtered from their cultures, generally in extracts of malted grain; they are often mixed with starch to the proper consistency. The living cells have long been used as a bactericidal dressing for ulcers and boils, but are not effective (Schugt, 1921). The discovery of vitamin B in yeast (McCollum *et al.*, 1916) aroused fresh interest. The administration of living, dried and autolyzed yeast or extracts increases the thiamine and riboflavin content of the diet; but the thiamine of raw yeast is only 17 per cent utilized (M. Hochberg *et al.*, 1945); its availability is strikingly increased by boiling (H. T. Parsons *et al.*, 1945). Rather large doses of yeast are effective against human beriberi (although less active than rice-hull extract, Saleeby, 1919) and the polyneuritis and malnutrition of polished-rice disease, and in pellagra. Yeast has been widely advertised with exaggerated claims as a cure for digestive derangements, constipation, boils and as a general "tonic." Critical experiments are generally disappointing, and its use may cause considerable digestive disturbance.

Living and perhaps also dead yeast cells are *laxative* (F. A. Brown *et al.*, 1934), but it is questionable whether they should be preferred to the medicinal laxatives that are better understood. The administration of yeast is sometimes followed by the relief of *acne,* furunculosis, herpes, etc.; but the results are so inconstant that it is not possible to judge how far they are due to coincidence or to other factors, such as the catharsis, the high content of nucleic acid, etc. (Tsuru, 1909; Abraham, 1910). The dosage is from 1 to 20 Gm. of the "compressed yeast" per day. Yeast extracts resemble "meat extracts" in taste and may be used to flavor soups and bouillons. Yeast has been proposed as a *nitrogenous food;* but its protein value is not high, a large part escaping by the feces. Its high purine content tends to raise the uric acid of the blood (Funk, Lyle and McCaskey, 1916). Caution should be observed in administering yeast continuously; for Osborne and Mendel, 1919, frequently observed degeneration of the testicles, with consequent sterility, in rats on a yeast-containing diet.

Yeast and Vitamins on Carcinogenic Substances.—In rats exposed to dimethyl amino azobenzene, the incidence of liver cancer is decreased by supplementing the diet with yeast (Kinosita, 1937) or with riboflavin plus casein (Kensler *et al.*, 1941). Yeast feeding also protects against other carcinogenic substances (Maisin and Pourbaix, 1938). Intravenous injection of yeast plus pantothenic acid inhibits spontaneous mammary cancer in mice more effectively than either agent alone. The addition of other vitamins had no effect (Lewisohn *et al.*, 1941).

PREPARATIONS.—*Dried Yeast*, U.S.P., Saccharomyces Siccum, consists of the dry cells of S. cerevisiae, a by-product of the brewing of beer, "brewers' yeast"; or from culture media, "primary dried yeast." Each Gram must contain not less than 0.12 mg. of thiamine hydrochloride, 0.04 mg. of riboflavin, and 0.25 mg. of nicotinic acid. *Dried Yeast Tablets*, U.S.P., are usually available as 0.5 Gm.

NUCLEOTIDES

Injection of nucleic acid salts (derived from the nucleoproteins of nuclear material, usually prepared from yeast) produces temporary leukopenia, followed by marked leukocytosis, involving chiefly the polymorphous neutrophils. The leukocytosis is chiefly of peripheral origin; but there is also hyperplasia of the bone marrow. This may be maintained by repeated injections, at least for a time, without becoming either exhausted or excessive (literature in Doan, Zerfas *et al.*, 1928). The leukocytosis has been used to combat malignant neutropenia (Jackson, Parker and Taylor, 1932), with somewhat doubtful success.

Das Gupta considers that it has not been proved that pentnucleotide or liver extract accelerate the formation of white cells, and believes that the reported transient pentnucleotide leukocytosis is due mainly to redistribution of the leukocytes. He believes that colchicine is the only drug that stimulates the proliferation of cells in the bone marrow, and that its toxic effects outweigh this stimulation. Good clinical response, however, has been reported in neutropenia following benzene, and gold thiocyanate, poisoning (Rheinheimer and Smith, 1933), but not many cases are on record. In rats poisoned with benzene it quickened the restoration of either the red or white corpuscles (C. Reich and Reich, 1934). The clinical improvement of the blood picture may begin in twenty-four hours, but generally does not become marked till the third to sixth day of administration, regardless of the previous duration of the illness. It then progresses till the normal is reached, perhaps about the tenth day. The fever which accompanies malignant neutropenia falls within a day after a marked increase of neutrophils has become established. Severe cases respond as well as the mild, or better. The delay in the response may account for some of the failures. Sometimes the increase of neutrophils leads to suppurations, such as pyelitis, presumably by making possible a leukocytic response to a preexisting irritation (Jackson, Parker and Taylor, 1932). It has been suggested to increase the neutrophils above the normal to combat other infections (Chantemesse, 1907, tried this for tuberculosis), but the value has not been demonstrated. Rather crude extracts and digests of yeast were employed originally. Recently more refined preparations, especially *pentose nucleotides*, have come into use, with the advantage that the effects may be better controlled. Guanine nucleotides, adenine, and pure adenyl guanidic acids also produce considerable neutrophilia, but the preceding neutropenia requires a larger nucleic molecule (Doan, 1932).

Administration.—Pentnucleotide, N.N.R., is an 8 per cent solution (approximately) of the sodium salts of the pentose nucleotides (chiefly four) from the ribonucleic acid of yeast (*p*H 7.2). This is injected into the gluteal muscles, 10 cc. twice daily, till the white count has risen definitely, then once daily till the count has remained normal for three days. In desperately ill patients, these doses may be doubled. The upward trend of the white blood cells is usually recognizable about five days after starting the administration. Nucleins are not anaphylactic antigens (De Waele and van de Velde, 1932), but intradermal injection of nucleic acid, 0.008 mg., or its clearage products provokes a positive skin reaction in patients allergic to ragweed pollen, while normal individuals do not react to this dosage (Winkelwerder *et al.*, 1939). Intravenous injection of nuclein is not advised, since it causes considerable acute reaction (dyspnea, precordial distress, bradycardia and sweating). With intramuscular administration these reactions are absent or mild. *Adenine sulfate* has been used in neutropenia, with about equal success. It is administered by vein (0.5 to 1 Gm. per day) and therefore acts more promptly; perhaps with less colloidoclastic reaction than intravenous pentnucleotide.

Fate.—Nucleic acid passes the stomach unchanged. It is partly split in the intestines, with the liberation of phosphoric acid, but not of purines. A further part is presumably split during absorption (bibliography, Forbes and Keith, 1914). The *nucleins* are excreted as purine bases and uric acid; so that they are contraindicated in gouty and rheumatic conditions, etc. The phosphate elimination is also increased.

TOCOPHEROL (ANTISTERILITY VITAMIN E)

This substance is essential for the fertility of rats and mice in both males and females (Evans and Bishop, 1923), but apparently not for the larger domesticated animals (B. H. Thomas *et al.*, 1938) and probably not for man. J. C. Drummond, 1939, pointed out that the diet of the poorer people in England is notably deficient in this vitamin, but that they are prolific. Wheat germ oil, 0.25 to 6 cc. per day, has been reported effective against *habitual abortion*, menstrual disorders, failure of lactation, and vaginal pruritus, but the results lack convincing clinical evidence, and unfavorable effects, gastro-intestinal irritation and skin rashes sometimes follow the larger doses. They are rarely serious (review, S. W. Clausen, 1940). Tocopherol has also been employed in muscular *dystrophies and spinal cord lesions*, with doubtful results.

Chemistry.—The protective substance occurs in the oil of wheat germ and other seeds, fresh vegetables (lettuce), fruits and many other foods. It was isolated by H. M. Evans *et al.*, 1936. It was identified as an alcohol, $C_{29}H_{50}O_2$, and named tocopherol. It exists as three modifications, which occur together. The alpha form was synthesized by Karrer, 1938. One of its decomposition products, durohydroquinone and its ethers, produces the same effects (Evans *et al.*, 1938). The tocopherols are potent *antioxidants*, preventing rancidity of fats (Olcott and Mattill, 1941). Tocopherol appears to be stored tenaciously; a single large dose allows fertility for two gestations but not for three (Olcott and Mattill, 1934). Spectroscopic studies of rats fed with tocopherol show its presence in the leg muscles, with high doses also in the adipose tissue, but not in the liver (Culbertson, Ridgeway and Drummond, 1940). Continued oral administration in myopathies raises its concentration in the serum from about 0.65 mg. to 2 mg per cent (Wechsler *et al.*, 1943).

Tocopherol deficiency effects differ materially in various animals. The principle phenomena are failure of early embryonic development in rat and mouse; irreparable degeneration of germinal epithelium in male rat (Mattill and Stone, 1923); degeneration of skeletal muscle in most species; nutritional encephalopathies in chicks. Rats also show retarded growth, straddling gait, coarse hair (reviews, Wolbach and Bessey, 1942; A. M. Pappenheimer, 1943), and progressive loss of pigment from the incisors (Granados and Dam, 1945).

The death of the developing embryo in rats and mice is due to limited development of the placenta. The fetus dies with widespread hemorrhages when about two-thirds of the gestation is reached. Some discoloration and degeneration of the uterine muscles have been reported, and uterine fibrosis and fibromyomata may result if the deficiency is protracted (Barrie, 1938; Martin and Moore). *Eggs* laid by hens on an E-deficient diet also do not develop living embryos, but die about the tenth day (Mattill, review, 1938). They show excessive cell proliferation in the mesoderm, obstructing the blood vessels of the blastoderm (Adamstone, 1931).

Muscular dystrophy and spinal cord lesions, resembling amyotropic lateral sclerosis and tabes dorsalis, result in rats with vitamin E deficiency, and are cured by alpha tocopherol (M. Goettsch and Pappenheimer, 1931; G. C. Knowlton *et al.*, 1939). They occur also in other mammals. Tocopherol apparently plays an essential role in the metabolism of skeletal muscle. Deficiency produces extensive necrosis (H. S. Olcott, 1938), resembling the hyaline degeneration of infectious diseases. Cod liver oil increases the degeneration (C. G. Mackenzie *et al.*, 1941). Widespread degenerative changes in the central nervous system have been described (M. Lipschutz, 1936; Einarsen and Ringsted, 1938), but the evidence is not satisfactory. Smooth muscle is not affected (review, A. M. Pappenheimer, 1943). Administration of tocopherol and of wheat oil has been *tried clinically in neuromuscular disorders*, but the results are disappointing (A. J. Lubin, 1942). The "*encephalomalacia*" *of chicks*, resulting from E-deficient diet, involves cerebral ischemia associated with impairment of the blood vessels (A. J P. Martin and Moore, 1938).

Alpha tocopherol acetate quickly cures *capillary fragility* and purpura induced in dogs by stilbestrol. Human thrombocytopenic purpura is also benefited by 200 to 400 mg. daily, after one or two weeks, but its administration must be continued indefinitely (F. Skinner, Shute *et al.*, 1946).

Large doses of tocopherol orally are not toxic to animals (Demole, 1939); nor does long-continued administration produce *sarcoma* in rats (Dingemanse and van Eck, 1939; H. M. Evans and Emerson, 1939), as has been claimed.

Vitamin F.—This term was applied by Evans to unsaturated fatty acids of lard and butter, which appeared necessary for the continuance of gestation and for the prevention of sterility in males. The designation was then transferred to linoleic acid, in respect to its effects on the skin. It has been dropped.

Vitamin K is discussed in connection with blood coagulation (see Index).

CHAULMOOGRA OIL

This fat, which is expressed from the seeds of East Indian trees of the genus Taraktogenos and Hydnocarpus, consists of the glyceryl esters of a unique series of cyclic fatty acids. These possess a specific toxicity for acid-fast bacteria. It has been reported that the administration of these acids and their esters appears to stay the progress of clinical leprosy, producing recession of the nodular, macular and anesthetic lesions, and the degeneration and disappearance of the bacilli, so that a considerable proportion of the cases can be paroled as apparently cured. The disease tends to recur, however, and it is itself subject to temporary intermissions from a variety of causes, so that the effectiveness of the treatment is difficult to appraise and critical observers doubt whether the course is better than with patients who do not receive the drug (review, G. W. McCoy, 1942). The amenability decreases with the duration of the disease. The oil has been used in India against leprosy since antiquity; but the nauseating taste and the gastro-intestinal irritation render intensive medication by mouth difficult. Weekly intramuscular injection of the ethyl-esters of the fatty acids is better tolerated. The treatment must be continued for a considerable time. Chaulmoogra oil has also been suggested for the treatment of tuberculosis, but there is no convincing evidence of its clinical value, and the results of animal experiments were negative. Good results have been reported in lupus. It has been used as an anthelmintic in the Orient since antiquity, but is not employed for this purpose by modern physicians.

Composition.—F. B. Power *et al.*, 1904 to 1907, confirmed by A. L. Dean and Wrenshall, 1920, showed that true chaulmoogra oil consists principally (90 per cent) of the glycerides of a series of unsaturated fatty acids which are unique in that they contain a closed 5-carbon ring, are optically active, and have not been found in any other oils. The most abundant of these acids are *chaulmoogric acid*, and *hydnocarpic acid*, which contains 10 CH_2 in the side chain, instead of 12. The structural formula was established by Shriner and Adams, 1925, confirmed by synthesis, and various homologues prepared. Their actions on the leprosy bacillus are qualitatively similar, but the hydnocarpic is somewhat more active. There are also small quantities of other homologues. Roger Adams and his associates synthesized other cyclic fatty acids and found these more or less effective against the leprosy bacillus. C. D. Leake, Anderson and Emerson, 1934, tested a number of the esters on rat leprosy (the identity of which with clinical leprosy is not established), and compared this with the toxicity and local irritation, and the lethal action *in vitro*. The most effective contain the cyclopentyl group, are optically active and possess the highest degree of unsaturation. Ethyl chaulmoograte ranked high (Anderson, Emerson and Leake, 1934). The oil contains also small quantities of ordinary fats, which do not participate in the action. The oil of Gynocardia odorata, which has been confused with chaulmoogra oil, does not contain the cyclic fats, and is inactive (Schoebl, 1924).

Historical.—The first attempts to obviate the oral administration utilized the hypodermic or intramuscular injection of the oil, generally thinned by the addition of olive oil (for instance, V. G. Heiser, 1913). This produced severe local irritation. Leonard Rogers, 1916, used the sodium salt (soap) subcutaneously and intravenously; this also gave good response, but often led to obliteration of the vein. The ethyl esters were prepared by Hollmann and Dean, 1919, and applied by McDonald and Dean, 1920, at Honolulu. Although these are less irritant, they often produce febrile reactions and vein sclerosis. Further references can be consulted in Walker and Sweeney, 1920.

Clinical improvement is seen only in part of the patients. It is described as disappearance of the macules; initial swelling of the nodules, then softening, contraction, and complete cicatrization; improvement of sensation; decreased swelling of the nerves; healing of the ulcers; disappearance of the bacilli from the nasal mucus and the blood of the macules; improvement of general health. The response of early cases requires three months of energetic treatment; three to six months with moderately advanced cases. Old cases do not respond. Relapses tend to occur when treatment is stopped, even if it has been continued for years. Similar improvement may occur without chaulmoogra, but only exceptionally, according to those who are convinced of its value; in about the same ratio, according to the skeptical (comprehensive review, H. Schlossberger, 1937).

Renal Damage.—Toxic doses or hypodermic and intravenous injection of sodium hydnocarpate, and also of the ethyl esters, are reported to produce hemolytic anemia, nephritis, albuminuria, hematuria, fatty degeneration of the liver and emaciation in rabbits and dogs (B. E. Read, 1933). Repeated intravenous injections into rabbits resulted in parenchymatous degeneration of the kidneys and liver (C. N. Frazier, 1931)

Focal reactions, intensification and irritation of the local lesions, febrile symptoms, and sometimes anaphylactoid phenomena (F. L. McDaniel, 1924) may occur, and some observers consider them essential for therapeutic results (E. Muir *et al.*, 1923). Latent tuberculosis may be activated. Softening and resolution of the lesions is reported in rat leprosy, but they are not cured.

The *fatal dose* is fairly high, even with intramuscular injections. Intravenous injections kill with smaller doses by hemolysis.

Febrile Reaction.—With the modern intensive administration, about 10 per cent of the patients develop skin eruptions and fever, beginning one to three days after the injection and disappearing in two to three weeks. The reaction is not serious, but may require interruption and slowing of the treatment (McDonald, 1920). It is probably due to the liberation of toxins by the reaction of the bacteria and tissues.

Bactericidal Action in Vitro.—Chaulmoogra oil and the sodium salts of its fatty acids are about a hundred times more potent than is phenol against tubercle bacilli and other acid-fast bacteria, while other bacteria are not susceptible (Hernandez, 1918; Walker and Sweeney, 1920). The potency appears connected with the fatty and waxy nature of the acid-fast envelope, which is presumably altered by these acids. This again is connected with their cyclic structure and not with their unsaturated characters; for the soaps of linoleic acid and the cod liver oil lack the specific toxicity.

Dosage of the "Ethyl Chaulmoograte."—This consists really of the esters of the mixed acids. McDonald uses it in weekly injections into the upper and outer quadrant of the gluteal region, alternating the sides weekly. The first injection is of 1 cc., increased by 1 cc. every second and third injection, until the maximum of 3 to 5 cc. is reached. Resistant lesions may also be injected directly with the ester. The injection produces some pain and irritation, and sometimes necrosis, but much less than the oil (Voegtlin *et al.*, 1921). The irritation is due partly to impurities and decomposition products of the raw oil. Abscess is exceptional. There is generally no digestive disturbance.

Oral Administration of Ethyl Chaulmoograte.—The dose is increased gradually from 1 to 5 cc. per day, after meals, in warm milk or hot tea. It is tolerated much better than the oil, and over longer periods, since its taste and odor are not disagreeable and it does not disturb digestion.

Oral Administration of Chaulmoogra Oil.—The dosage begins with 0.3 cc. three times daily, and is increased to the point of tolerance. Various methods are described by B. E. Read, 1925. The emetic action is reflex and may decrease on continued administration. *Overdosage* may cause dyspnea, laryngeal spasm, renal irritation, weakness, and intensification of the lepra lesions.

Intramuscular administration of chaulmoogra oil is quite painful and seriously irritant, and easily produces necrosis at the site of injection (Voegtlin *et al.*, 1924; Cadbury, 1920). Absorption of the oil and esters is even slower than with ordinary oils, because of the inflammatory reaction (Valenti, 1917). The oil must be thinned by the addition of olive oil, and analgesics are usually added, as in the "Heiser Mixture," equal parts of chaulmoogra and camphor oil, with 3.6 per cent of resorcin. It is injected weekly, increasing from 2 to 10 cc. *Intravenous injection* of the esters is dangerous, as it may result in pulmonary embolism (Walker *et al.*).

Sodium Soap.—The intravenous injection, according to Rogers, 1917, produces temporary giddiness, headache and occasional occlusion of the vein, preventing its further use. According to Voegtlin *et al.*, 1921, this is due to the alkalinity of the soap, and is a serious objection. Rapid injection of the 2 per cent solution also produced embolism.

Tuberculosis.—The similarity of the bacilli suggested to Rogers, 1916, that chaulmoogra oil might be efficient in tuberculosis. The experiments of Voegtlin *et al.*, 1920, failed to reveal any effect on the weight, growth, lesions and mortality rate of a large series of tubercle-infected guinea pigs.

PREPARATIONS.—*Chaulmoogra Oil,* U.S.P., a fixed oil expressed from the ripe seeds of Taraktogenos or Hydnocarpus species. Average dose, 1 cc. *Ethyl Chaulmoograte,* U.S.P., insoluble in water, miscible with alcohol. Average dose, oral or intramuscular, 2 cc.

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EMOLLIENTS, DEMULCENTS AND PROTECTIVES

These are chemically indifferent substances that are used to cover and thus to protect surfaces against drying and other irritation. Oils, fats and glycerin, when so applied to the skin, also tend to soften the epidermis and are therefore termed emollients (*emollire,* to soften). When applied to mucous membranes or wounds, protectives are designated as demulcents (*demulcere,* to smooth down), since their main purpose is to soothe irritation. Viscid water-miscible solutions, for instance, of the gums, or glycerol, adhere to these moist surfaces better than does oil. This corresponds to the natural mechanisms for the protection of the body surfaces: While the skin is normally covered with a thin layer of emollient oil, the mucous membranes of the interior of the body are moistened with mucus, which is a gummy demulcent. Fine insoluble and adhesive powders, such as talcum, are also used as demulcents of the skin and mucous membranes. The protectives diminish the local action of chemical, mechanical or bacterial irritants, decreasing pain, reflexes, catarrh, spasm and other manifestations of irritation. They delay and diminish absorption from the stomach, intestine, subcutaneous tissue, etc. This diminishes the systemic effects of absorbable poisons and prolongs their local actions.

Mechanism of Action.—Colloids and fats are practically indifferent and unabsorbable for cells, so that they do not produce direct effects on them; but, through their adhesive character, they form a covering and hinder the access of irritant agents. Oils prevent the penetration of water-soluble substances; gums, that of fats and resins. Gums also diminish the effects of crystalloids by increasing the viscidity of the solution, thereby interfering with its transportation (von Tappeiner, 1902). Adsorption probably also plays a part, for dissolved substances are condensed on the surfaces of fine powders and thus removed from the solution.

Emollient drugs comprise the true fats and oils (glycerides of fatty acids), wool fat, petrolatum and glycerin. They are applied as a protective dressing to the skin, ulcers, burns and other superficial wounds; as vehicles (salves) for the application of medicaments to the skin or, more rarely, for systemic effects (mercurial inunctions). Internally, the true fats serve as nutrients. Larger amounts than can be digested stimulate peristalsis and act as intestinal lubricants and laxatives. For external use, the liquid or soft fats should be chosen when the preparation is to be rubbed into the skin glands, whilst protection and prolonged contact are secured by the harder and more adhesive ointments, wool fat and petrolatum mixtures, cerates and plasters. Petrolatum alone is not very adhesive. All the ointments and glycerol tend to soften the epidermis, by preventing drying. In this they aid the natural oil of the skin and prevent roughness and "cracks" from wind, cold weather, sunburn or skin diseases. On hairy areas or those subject to friction or sweating, greases may lead to folliculitis by blocking the follicles. In such locations it is preferable to apply drugs as lotion or "vanishing creams."

Penetration of the Skin.—Fats and oils are not absorbed by the epidermis, but they may be spread so thin over the surface that they become invisible, and a small quantity may be rubbed into the hair follicles and gland ducts, liquids more rapidly than solid fat (Eller and Wolff, 1939), and can eventually be demonstrated microscopically in the lymph channels. True fats are slowly oxidized and disappear; but the mineral fats remain indefinitely in the subcutaneous tissue and produce chronic irritation and fibrosis. Animal and vegetable fats therefore deserve preference when penetration is desired (Sobieranski, Juckuff, Meyer).

Absorption through the skin occurs almost entirely from the gland ducts and hair follicles. The dead, desiccated and cornified cells which constitute the stratum corneum are not easily penetrated, and are futhermore covered by a greasy layer of lipid, chiefly esters of cholesterol and fats (M. L. Higgins, 1943). The skin is relatively impermeable to electrolytes. It is generally permeable to gases, but carbon monoxide is an important exception. The maximal absorption of oxygen by the skin is only a hundredth of that by the lungs (G. Zuelzer, 1904).

Fats on Penetration.—Fats and oils protect the skin against the penetration of fat-soluble irritants, such as phenol, mustard oil or "mustard gas" (Sollmann, 1918, 1919). On the other hand, oiling of the skin hinders the access of watery solutions to the epithelium (Filehne and Biberfeld); but ointment may increase absorption by retaining the sweat and preventing the normal evaporation of water (S. Rothman, 1921), and so macerate the cornified cells as to increase their permeability. Application of fat solvents, however, generally increases absorption from watery solutions (strychnine, R. Winternitz, 1891; insulin, S. Hermann and Kassowitz, 1935).

Rancidity.—Fats turn "rancid" on keeping, especially if exposed to air, light and heat, or if they contain protein impurities. The change consists in oxidation with the development of free volatile fatty acids. Rancid fats are disagreeable and irritating. Petroleum products are free from this objection, but rancidity may be avoided with other ointments by keeping and dispensing them in air-tight "tin tubes."

Oil-Aspiration (Lipid) Pneumonia.—Oil "drops" instilled into the nose or nasopharynx may be aspirated into the trachea and lungs. This occurs also with laxative mineral oils, especially in infants and debilitated patients. It causes little, if any, immediate disturbance, but if it is often repeated it gives rise to chronic recurrent inflammation of the respiratory tract. This varies greatly in severity according to the kind and amount of the aspirated oil. Animal oils produce more severe lesions than mineral oils. Infants show interstitial proliferative inflammation and quite commonly exudative pneumonia, the "lipid pneumonia" of I. Graef, 1939, and eventually fibrosis. Organized granulomatous lesions are more frequent in adults (review, P. R. Cannon, 1940).

OLIVE OIL AND OTHER BLAND FATTY OILS (OLEA PINGUA)

The expressed oils of olive, cottonseed, almond, sesame, etc., are essentially similar. Olive oil is preferred for internal use because of its more agreeable flavor. These oils are employed externally to soften the skin and crusts in eczema and psoriasis; as dressing for burns; as vehicles for liniments, etc.; and by rectal injection, to soften fecal concretions (150 to 500 cc., 5 to 20 ounces, of the cheaper cottonseed oil, warmed. Hertz claims that oil is less effective than water for this purpose). Internally, olive oil is used as nutrient, laxative, and in hyperchlorhydria (15 to 50 cc., ½ to 2 ounces before meals). Kennedy and others claimed beneficial results in biliary colic, using large doses (150 to 500 cc. in four to eight portions within three hours). The concretions found in the feces when olive oil and Epsom salt are given are not gallstones, but soap (magnesium oleate). Fats are useful antidotes in corrosive poisoning. The protective action of oils against irritation and absorption was known and used by the Greek physicians. These oils are insoluble in water or glycerol, sparingly in alcohol, freely in chloroform, ether, volatile oils, or fats.

Influence on Digestion.—Neutral fats allay gastric peristalsis, diminish gastric secretion and acidity (Pavlov; Chiari, 1915), and lessen the pyloric tone. They leave the stomach slowly and in small portions; a fatty meal requires seven hours for complete passage into the duodenum. The digestibility of animal fats is discussed by Langworthy and Holmes, 1915. The length of gastric sojourn increases with the melting point of fat (Feyer, 1913). Clinical doses of olive oil do not affect the acidity or emptying time of the stomach (F. L. Apperly, 1943). In the duodenum, fats check the gastric discharge and stimulate the flow of pancreatic juice and the evacuation of the gallbladder (review, Ivy, 1934).

Subcutaneous injections of fats as nutrients were proposed by Leube, 1895, but the absorption of plain fats is too slow to be of practical value (Winternitz, 1903). Somewhat better results were obtained with fats emulsified by lecithin (Mills and Congdon, 1911). The injection of free fatty acids would be toxic. Fats are also oxidized when emulsions are injected into a vein (Murlin and Riche, 1915).

Oleic Acid Anemia.—Continued administration of large doses of oleic acid, by mouth or hypodermically, to animals produces hemolysis and severe anemia (Faust, 1906 and 1908; Adler, 1911). Similar effects produced by the injection of extracts of tapeworm (bothriocephalus) are also attributed to oleic acid-cholesterin esters (Faust). However, Klotz and Spencer, 1917, did not observe any changes in the number or structure of the blood corpuscles after two weeks of intravenous injection of suspensions of cholesterin in sodium oleate. The saturated higher fatty acids are also hemolytic (Shimazono, 1911). The hemolysin of bacterium putridum is oxydimethyl thiol-erucic acid, a typical unsaturated fatty acid (Burckhardt, 1910).

Atopic Reactions.—Asthmatic attacks in atopic individuals have been reported as the result of contact or ingestion of linseed oil (Taub and Zakon, 1935) and cottonseed oil (Coca).

PREPARATIONS.—***Olive Oil**, U.S.P. (Oleum Olivae; Sweet Oil), is a pale yellow or greenish-yellow fixed oil, expressed from the ripe fruit of Olea europoea. Dose, 30 cc., 1 ounce.

Oleic Acid, U.S.P. (Acid. Oleicum), is an oily liquid acid, chiefly $CH_3(CH_2)_7CH{:}CH(CH_2)_7.COOH$, obtained from tallow and other fats. Yellowish or brownish yellow; peculiar lardlike odor and taste, practically insol. in water; miscible with alcohol, chloroform, and with fixed and volatile oils. Used as solvent for metallic oxides and alkaloids intended to be absorbed from the skin.

Cottonseed Oil, U.S.P. (Ol. Gossypii Seminis), is a pale yellow fixed oil expressed from seeds of cultivated varieties of Gossypium. Slightly soluble in alc. On account of its cheapness, it is especially adapted for external use. It is inferior for internal administration; it can not be readily emulsified or saponified, since the free fatty acids have been removed in the process of purification. Feeding with "*cottonseed meal*" (not the oil) sometimes produces toxic effects. These are due to *gossypol*, a crystalline substance, $C_{30}H_{30}O_8$, first isolated by Marchlewski, 1899. It is insoluble in water, soluble in dilute alkali, in oils and in gasoline. It may be rendered harmless by autoclaving the cottonseed meal at 15 to 20 pounds for several hours and by various methods of oxidation, precipitation or extraction (Withers and Carruth, 1915). The *phenomena of cottonseed poisoning,* as observed in the slow poisoning by feeding farm or experimental animals (dogs, rabbits, cats, less typical in rats), consist of diarrhea, loss of appetite, emaciation, edema of the lungs and shortness of breath, edema of the anogenital region, neuritis and paralyses. The disturbance of digestion and nutrition is due to intestinal impaction and enteritis, which is severe and may be hemorrhagic. Injections of alkaline or oily solutions produce marked irritation and edema at the site of injection. Intravenous and intraperitoneal injections cause congestion and hemorrhages in the viscera, cardiac dilatation and death from pulmonary edema. Less characteristic direct effects on the heart and excised intestine have been described. Cottonroot bark, which also contains gossypol, has been used as abortifacient (see Index), but does not seem to be very effective (Schwartze and Alsberg, 1924; E. P. Clark, 1927). The toxic properties of *Tung nuts* were studied by Erickson and Brown, 1942.

Other Fatty Oils are Expressed Almond Oil (Ol. Amygdalae Expressum); Peanut Oil (Ol. Arachis); Linseed Oil (Ol. Lini); Corn Oil (Ol. Maydis); and Sesame Oil (Ol. Sesami; Teel Oil, Benne Oil); Persic Oil, expressed from the kernels of apricots or peaches.

Theobroma Oil, U.S.P. (Ol. Theobromatis; Cacao Butter), is a yellowish-white solid fat from the roasted seeds of Theobroma Cacao. It melts at the temperature of the body. It is used mainly for making suppositories, as a lubricant in massage, and for cracked nipples. It is not to be confused with *Oleum Cocos,* the expressed oil of the coconut, the fruit of the palm, Cocos nucifera. It is a whitish fat, soluble in alcohol, used especially in soap making.

SOFT ANIMAL FATS

These are employed as ointment bases. They have the inconvenience of rapidly turning rancid. This is delayed by antiseptics, as in Benzoinated Lard.

Preparations.—*Benzoinated Lard,* U.S.P. (Adeps Benzoinatus), is lard (the purified internal fat of the abdomen of the hog) impregnated with 1 per cent of Benzoin. It imparts to the lard a pleasant odor, the antiseptic and stimulant properties of the balsams, and increases its keeping qualities. Lard is insol. in water; slightly sol. in alc.; melts between 36° and 42° C.

Butter (Butyrum) and *Mutton Suet* (Sevum) are similar. *Other animals* also yield fats which are popularly supposed to have special advantages—dog fat, goose grease, etc. There appears to be no established reason for preferring them to the more easily obtainable lard.

WOOL FAT—LANOLIN

This differs chemically from ordinary fats in that the fatty acids are not united to glycerol but to cholesterol and isocholesterol and smaller quantities of other alcohols. Crude wool fat or suint was used by the ancients, but has a disagreeable odor. A purified hydrated product was introduced by Liebreich as "lanolin." Even this has a rather unpleasant odor and disagreeable sticky consistence, but it does not readily turn rancid. Since its composition resembles that of the natural skin fat, it was believed that it would be more readily absorbed; but this does not seem to be the case. Its chief advantage lies in the property of forming salvelike emulsions with up to two or three times its volume of water, so that watery solutions may be incorporated with it. In contrast to ordinary emulsions, the water is the dispersed and the lipid the continuous phase. Considerable quantities of true fats or petrolatum may be mixed with the wool fat without destroying this quality. Anhydrous wool fat melted with three parts of petrolatum can be mixed with at least twice its weight of water. Anhydrous wool fat is too "doughy" for ointments; it is employed after the admixture of 30 per cent of water (Hydrous Wool Fat), or better with the further addition of an equal weight of petrolatum or other fat. Ointments containing wool fat are more adhesive and coherent than ordinary fats, more suitable for prolonged effects, but less so for inunction.

Wool fat consists of a mixture of cholesterol esters and of alcohols of the fatty series, including ceryl alcohol. Its fatty acids are largely those of ordinary fats (E. Rohmann, 1916). Wool fat is *not absorbed* from the intestines (Bloor, 1913).

Preparations.—***Hydrous Wool Fat,** U.S.P. (Adeps Lanae Hydrosus; Lanolin), is the purified, fatlike substance from sheep's wool, containing 25 to 30 per cent water. It occurs as a yellowish-white ointment-like mass, having no more than a slight odor; is sparingly sol. in alc., insol. in water, but is miscible with about twice its weight of water. The Anhydrous *Wool Fat,* U.S.P. (Adeps Lanae; Anhydrous Lanolin), is a light yellow, tenacious, unctuous mass, melting between 36° and 42° C., insoluble in water but mixing with up to two parts of water without separation; sparingly sol. in alcohol.

COMPOUND OINTMENT BASES

These differ chiefly in consistence and miscibility. One of the most useful is the mixture of equal parts of hydrous wool fat and petrolatum, a water-in-oil emulsion that mixes both with fat and with moderate quantities of water. *White Ointment,* U.S.P., consists of white petrolatum with 5 per cent each of wool fat and white wax. It is also miscible with considerable water. "*Yellow Ointment,*" U.S.P., similarly contains 5 per cent each of wool fat and yellow beeswax, and 90 per cent yellow petrolatum. The U.S.P. authorizes adjustment of the proportions of the vehicle ingredients of its ointments to climatic conditions. *Cerates* are stiffer ointments containing sufficient wax so as not to melt at body temperature. *Simple Cerate* (Ceratum, U.S.P.) is composed of benzoinated lard and white wax. In *Rosin Cerate,* U.S.P. (Cerat. Resinae, Basilicon Ointment), lard is stiffened with yellow wax and rosin. *Toilet creams* are soft ointments used for protection and cleansing. *Cold Cream* (Ung. Aquae Rosae, U.S.P.) is a water-in-oil emulsion made with expressed almond oil stiffened with white wax and spermaceti (a fat from the skull cavity of the sperm whale, chiefly cetyl palmitate), emulsified with 0.5 per cent of borax, flavored with oil of rose. *Hydrophilic Ointment,* U.S.P., consists of white petrolatum and stearyl alcohol, 25 per cent of each, incorporated into water and glycerin by synthetic emulsifiers. It is cooling by the evaporation of its water. Many modifications exist; a typical formula was given by Galen.

Emollient creams are cold creams, generally with some wool fat. *Vanishing creams* (foundation creams) are emulsions of stearic acid in water, made with soap. They contain 70 to 90 per cent of water, which evaporates from the skin, leaving a very thin film of stearic acid, which serves as an adhesive surface on which to spread powders. *Cleansing creams* are maximally superfatted soaps (Fantus, 1936). *Protective films* used by mechanics and painters as "invisible gloves" against soiling with grease, paint or varnish, and as protection against chemical irritants, consist of paste of sodium silicate and soaps, often with casein. They prevent access of dirt and wash off easily.

WAXES AND WAXLIKE FATS

These are used in pharmacy mainly to stiffen ointments (as in cerates).

Preparations.—These include *Yellow Beeswax,* U.S.P. (Cera Flava); *White or Bleached Beeswax,* U.S.P. (Cera Alba); *Spermaceti,* U.S.P. (Cetaceum), a pearly-white, fatty substance obtained from the head of the sperm whale; *Stearic Acid,* U.S.P. (a mixture of fatty acids, chiefly stearic and palmitic, sol. in 20 parts of alcohol); *Stearyl Alcohol,* U.S.P., a mixture of solid alcohols, chiefly stearyl alcohol; *Sodium Stearate,* a mixture of varying proportions of sodium stearate and palmitate; *Rosin,* U.S.P. (Resina; Colophony), is the amber-colored residue left after distilling off the volatile oil from turpentine, the concrete oleoresin obtained from species of pine.

PETROLATUM AND OTHER PETROLEUM PRODUCTS

"Mineral fats" are mixtures of hydrocarbons obtained from petroleum by fractional distillation, chilling, purification by filtration through bone black, etc. They consist of hydrocarbons of the methane and related aliphatic series. According to the process of preparation, they occur in various consistencies, from the waxy "paraffin" (employed for hardening ointments), through the buttery "petrolatum" (a typical emollient), to the "liquid paraffin" (used especially for laxative and sprays). The color, from deep yellow to almost pure white, does not affect the action, except that dark red petrolatum protects the skin against *sunburn* (Luckiesh *et al.,* 1946). Notwithstanding the chemical difference, they resemble the fats in physical character and therapeutic application. They have the advantage that they are chemically indifferent, do not undergo deterioration, can not become rancid or irritant, and do not react with drugs, such as oxidizing or reducing agents. They are not so well adapted for inunction.

Liquid Petrolatum as Laxative.—Only minimal amounts of mineral oils are absorbed from the digestive tract (Channon and Collinson, 1929). By far the greater part is eliminated unchanged by the feces (Randolph, 1885; Hutchinson, 1899; Bloor, 1913). They can not, therefore, act as nutrients. By softening the feces, they are mildly laxative, and are used as such in intestinal stasis (A. D. Schmidt, 1905; Lane, 1913). Sometimes they do not mix well with the feces, the oil leaking from the anus. Occasionally they induce nausea and regurgitation (Bastedo, 1914). They interfere materially with the absorption of carotene, vitamins D and K, calcium and phosphate, so that continuous use is not advisable. There is no evidence that they are carcinogenic (Council of Foods, 1943, J.A.M.A., *123:*967). Any of the "liquid paraffins" (Petrolatum Liquidum Album) may be employed—there being no therapeutic difference between the light or heavy Russian or American oils (Bastedo, 1915). Their composition is perhaps also similar. The usual dosage is from 10 to 30 cc., one-half hour before meals; or a single dose of 30 to 60 cc. before retiring. The "light" oil is preferred for sprays (Wilbert, 1914); the more viscid oils for laxatives. All oily sprays and insufflations interfere with ciliary movement. Repeated aspiration of liquid petrolatum "nose drops" or laxatives gives rise to chronic hyperplastic bronchitis and *lipid pneumonia* (see Index); 100 to 120 cc. of oil were found in the lungs after 20 years' use of nose drops.

Composition of Liquid Petrolatums.—All crude petroleum oils are complex mixtures of hydrocarbons, the composition varying quantitatively according to their origin. The constituents likewise vary with the origin. In North America they are chiefly of the aliphatic series; in Borneo and Sumatra, of the aromatic series; and in Russia, both series. These differences are eliminated in refining, so that the composition of the thoroughly refined, colorless products is probably similar, whether the product is derived from Russian or from American oils. The liquid petrolatums consist mainly of naphthenes (C_nH_{n-2}) and polynaphthenes (C_nH_{2n-2} and C_nH_{2n-4}). They do not contain true paraffins (C_nH_{2n+2}); so that the term "Paraffin Oil" is a misnomer. The irritant olefin hydrocarbons and the benzenes of the crude oils are absent from the refined. Certain ingredients, which give the fluorescence and rancid taste, are more difficult to eliminate from some oils than from others (Brooks, 1916) The history and composition are discussed in the J.A.M.A., 1914, *62*:1740.

Absorption and Metabolism of Paraffin.—Histologic evidence shows that a small amount is absorbed from the intestines in man as well as in rabbits, rats and guinea pigs, especially if the oil is emulsified with particles smaller than 0.5 microns. It is demonstrable in the mesenteric lymph nodes, liver and spleen (W. A. Stryker, 1941; A. C. Frazer *et al.*, 1942). N-hexadecane tagged with deuterium and fed to rats is fairly well absorbed, partially deposited in the tissues, and oxidized to fatty acids, apparently in the liver (De W. Stetten, 1943).

Paraffin Treatment of Burns.—Paraffin of proper plasticity may be used as dressing for burns, roentgen ray burns, and pruritus. A thin film of melted or liquid paraffin is painted on the clean surface, covered by a thin layer of cotton, and this again by a heavier coat of melted paraffin; then cotton, bandages, etc. The treatment obtained notoriety in the form of a secret preparation ("Ambrine"), but simple "surgical" paraffin is fully as good. The addition of antiseptics is useless, since they are hermetically sealed in the solid paraffin (Sollmann, 1917). Simple petrolatum dressing gave the most prompt healing of minor industrial burns (R. D. McClure and Lam, 1943). Liquid petrolatum is probably the best agent for the removal of fuel oils from burns and wounds.

Melted paraffin may also be used as a protective surface coating for ordinary dressings. Fisher, 1916, suggested the impregnation of bandages with paraffin mixtures to avoid adherence to wounds. Gauze impregnated with liquid petrolatum is not easily clogged by secretion, and therefore facilitates absorption by the dressings (Sollmann, 1917). N. Burns, 1917, reported erysipeloid skin eruptions following the use of liquid petrolatum, when insufficiently purified, as wound dressing.

Sterilization.—H. Lyman, 1917, suggested paraffin for sterilization of instruments; ten minutes at 150° C. kills even anthrax spores. *Mineral oil treatment of bedding and floors* retains bacterial dust (Loosli, Wise *et al.*, 1946). The bacterial count of the air may be reduced by 97 per cent, but cross infections are not reduced (Hollaender, 1946).

Paraffin Prothesis.—The persistence of the mineral fats in the subcutaneous tissue has been utilized for the *correction of deformities* (*e. g.*, of the nose), by injecting subcutaneously a mixture of paraffins melting at about 40° C. There is some danger of embolism, and the results are not permanent, the paraffin being gradually replaced by scar tissue (Heidingfeld, 1910), which may become a starting point for neoplasms.

Paraffin "Wax" Dermatitis and Cancer.—Continuous handling of unpurified paraffin may lead to dermatitis (Joseph, 1896), acne and other eruptions, papillomas and carcinomas. Mice and rats are also susceptible. Refined mineral oils, however, are not carcinogenic, even when used over long periods; nor do they produce irritation, for the carcinogenic agents are destroyed by the sulfuric acid used in the purification and also by other oxidizing and reducing agents. American crude oils are generally slightly carcinogenic (F. C. Wood, 1930; review, J.A.M.A., 1934, *102:* 1702).

PREPARATIONS.—*Paraffin*, U.S.P., melts between 50° and 57° C. It corresponds closely to Hard Paraffin, B.P.

**Petrolatum*, U.S.P. (Soft Paraffin, B.P.; Petrolatum Jelly), is a yellowish to light amber-colored semisolid mixture of hydrocarbons melting between 38° and 54° C. *White Petrolatum*, Petrolatum Album, has been wholly or nearly decolorized. *Hydrophilic Petrolatum*, U.S.P., contains white petrolatum, 73 per cent; wool fat, 15 per cent; white wax, 8 per cent; stearyl alcohol, 3 per cent; cholesterol, 1 per cent.

Petroleum (*coal oil, kerosene*) is somewhat irritant and narcotic. The clinical symptoms include local irritation, drowsiness, collapse, muscular twitching and coma. Myocardial insufficiency, hepatic and renal damage, and pneumonia may occur if death is delayed for several days. Pulmonary injury may result in rabbits from kerosene carried in the blood (Deichmann *et al.*, 1944). Its toxicity is generally low, and recovery has occurred after swallowing as much as a liter; but if it is aspirated into the lungs, as is liable to occur especially in young children, it may cause irritation pneumonia, so that six patients died in a series of sixty-five (Nunn and Martin, 1934). It should be treated by emesis and gastric lavage with olive oil or perhaps better with warm water, until the odor of kerosene becomes nearly imperceptible.

Gasoline (*petroleum benzin, petroleum ether, petroleum naphtha*) is a mixture of petroleum hydrocarbons distilling from less than 100° to about 400° F.; it contains various paraffins, olefins, naphthenes and benzene derivatives differing according to origin. Inhalation of the vapors causes headache, nausea, giddiness, inebriation, unconsciousness, muscular tremors, convulsions, dyspnea, cyanosis and death (Buergi and Burgl; Wolf, 1911). The inebriation, the "naphtha jag" of rubber factories, shows restlessness and excitement similar to alcohol intoxication, some subjects becoming happy and hilarious; others morose and quarrelsome. The excitement is followed by the after-effects of an alcoholic debauch: lethargy, sick headache, restless night, and morning nausea and misery. Addiction has been reported by inhaling the gasoline from a handkerchief. *Chronic poisoning* results in dulness, pain in the limbs, trembling, muscular weakness and other nervous disturbances (Rambousek), and pulmonary hemorrhages (Jaffe, 1914). E. R. Hayhurst, 1936, describes manifold bizarre symptoms. Blood changes are rare and damage to the blood is much less than with benzene. The symptoms of acute and chronic poisoning, as they occur in industry, are described by R. T. Johnstone, 1941. *Concentrated vapors* cause purely paralytic symptoms in frogs, but in mammals they have only a weak anesthetic action. Concentrations above 1:100 are rapidly fatal to most animals. Susceptibility varies considerably and some tolerance is acquired. If they are inhaled to the exclusion of air, they will cause an asphyxial anesthesia. Before this sets in there are very characteristic convulsions (Sollmann, 1904; Haggard, 1920). The animal struggles violently, then falls on its side and claws the air with all fours, as if running. The pupils are widely dilated. Reflexes are absent. The spasms are intermittent, and between them the dog is perfectly limp, except that the toes, tail and eyelids continue to twitch. The respiration is first stimulated, then weakened. There is paralysis of the vagus, then depression of the cardiac muscle, and later of the vasomotor center. Either heart or respiration may stop first. Gasoline is, therefore, unsuitable as an anesthetic even for animals; although it has been tried with man (Felix, 1888). In cats whose sympathetic tonus has been raised by epinephrine injection or by decerebration, petroleum ether is likely to produce ventricular rhythm, but less so than benzene (Nahum *et al.*, 1936). The most frequent changes at autopsy are visceral congestions and petechial hemorrhages, particularly in the lungs (W. Machle, 1941).

If gasoline is swallowed, it may produce similar narcotic symptoms (restlessness, incoordination, cyanosis) and some local irritation: intense burning sensation in the mouth and esophagus, vomiting, loose stools, sometimes bloody. Recovery occurs after a few hours of depression, unless gasoline has been aspirated into the lungs, in which case hemorrhagic pneumonia develops, often fatal in two to eighteen hours, sometimes after recovery from the acute effects. Serious poisoning may result from 20 to 30 Gm., and with children 10 to 15 Gm. may be fatal. The usual fatal dose for man is about 500 cc.; recovery has followed 250 cc. Of seven children who had swallowed gasoline, two died (Nunn and Martin, 1934). The treatment would be lavage with olive oil. Gasoline is absorbed slowly from the alimentary tract, and excreted mainly by the lungs (Jaffe, 1914).

"Ethyl gasoline," containing lead tetra ethyl, produces dangerous acute lead poisoning, even when it is absorbed from the skin.

PREPARATIONS.—*Petroleum Benzin*, U.S.P. (petroleum ether): hydrocarbons of the methane series, distilling completely between 35° and 80° C.; highly inflammable; vapor explosive.

GLYCERIN

Glycerin or glycerol acts both as emollient and demulcent. It is used to soften the skin, to prevent chapping, and internally against coughs. Concentrated glycerin abstracts water, so that the soothing action is preceded by smarting. It should therefore be diluted with two or three volumes of water (rose water for lotions). This, or a half volume of 70 per cent alcohol, also decreases its excessive viscosity so that it is more easily applied. Glycerin does not abstract water from the *intact* skin, because of the impermeability of the stratum corneum. Its absorption from the intact skin is negligible. On the *conjunctiva* 25 to 50 per cent glycerin causes brief smarting, followed by active hyperemia, lasting several hours. It is used in trachoma and cataract. Undiluted glycerin injected into the rectum causes evacuation in a few minutes, without pain if there are no abrasions (5 to 10 cc., 1 to 2 ʒ; of the official suppository). Similarly, it provokes uterine contractions if introduced into the cervical canal. Large doses (100 to 150 Gm. per day, in divided portions) have been employed to kill intestinal trichinae. Glycerin is used in pharmacy as a vehicle and solvent for salts; as a sweetening agent; to preserve ferments and vaccines; to keep pill masses or extracts moist, etc. As a sweetening agent in diabetes it has been displaced by saccharin.

Nutrient Value.—Glycerin is transformable into glycogen and sugar, after oxidation to 2,3-dihydroxypropanal (glycerylaldehyde); but its nutrient value is doubtful, since larger quantities diminish gastric secretion (L. Kast, 1910) and provoke diarrhea. Like other intestinal irritants, it produces increased elimination of uric acid (Abl, 1913); but with gross overdosage there may be acute damage to the liver, kidneys and lungs. Large oral doses injure the digestive tract. Diuresis is more pronounced with oral than with hypodermic administration.

The toxicity is low with oral administration. No deleterious effects were observed in man with 110 Gm. of glycerin per day for fifty days; indeed, the body weight increased. Normal growth and reproduction occurred in rats with 41 per cent of glycerin added to the food for forty weeks, in dogs with 35 per cent added for fifty weeks. No gross or microscopic changes of the viscera were seen after two years of high glycerol diet (V. Johnson *et al.* 1933).

Hypodermic injection of large doses causes convulsant and paralytic symptoms, presumably through direct action of glycerin on the central nervous system. The blood corpuscles are laked. This is probably an osmotic effect, the glycerin remaining for a time unabsorbed, and in high concentration at the place of injection, and the corpuscles being laked during their passage through this area (Filehne). Administration of ascorbic acid doubles the threshold dose of hemoglobinuria and lowers the mortality rate (Pfeiffer and Arnove, 1937). Intravenous injection of even small doses produces transient fall of blood pressure. Lethal amounts result in gradual failure of the circulation (review, Deichmann). On muscle-nerve preparations, glycerin acts like veratrine.

Antiseptic Action.—Concentrations of 25 per cent and higher are distinctly disinfectant, the efficiency increasing with the concentration. Undiluted glycerin destroys $\frac{8}{10}$ of the bacteria in three hours (Winslow and Holland, 1910). On the other hand, glycerin hinders the antiseptic efficiency of substances for which it is a better solvent than is protoplasm; for instance, thymol, phenol, mercuric chloride or boric acid.

Glycerin in Cigarettes.—Glycerin is added to cigarette tobacco as a hygroscopic agent. The irritant effects of cigarette smoke have been attributed to the acrolein produced by the combustion of the glycerol, and diethylene glycol has been substituted. Other observers, however, found no difference in carefully controlled tests (Haag, 1937; Holck and Carlson, 1937).

PREPARATIONS.—***Glycerin,** U.S.P., $CH_2OH.CHOH.CH_2OH$, obtained from the hydrolysis of fats, is a clear, colorless, thick, syrupy, sweet liquid; miscible with water or alc., insol. in ether, chloroform or oils. Dose, 4 cc., 1 drachm. *Glycerin Suppositories,* U.S.P., contain each 3 Gm. of glycerin for adults, 2 Gm. for infants, and are solidified by sodium stearate.

Glycerites are solutions of medicinal substances in glycerin.

GLYCERYL ACETATES

Mono-, di- and triacetyl esters of glyceryl are used as solvents in industry and pharmacy. The irritant action on the tissues, hemolysis and toxicity increase with the number of acetyl radicals (Li *et al.*, 1941). Technical triacetin contains all three esters. *Glyceryl Triacetate,* U.S.P. (triacetin), $(CH_3COO)_3C_3H_5$, is a colorless liquid, miscible with water and organic solvents.

GLYCOLS

These dihydric alcohols are related to glycerol in chemical and physical properties. They are better and more universal solvents and are widely used as such in industry, and as anti-freeze agents. Their use as medicinal solvents is limited by their toxicity, which culminated in the tragic mass poisoning by a diethylene glycol "elixir." This, and other glycols with an ether linkage of two glycol molecules, cause profound hydropic degeneration of the epithelium of the renal tubules and hepatic cords, leading to fatal uremia. Propylene glycol is the least toxic.

Glycol "mists" (finely divided sprays) have a decided *germicidal action* on air-carried bacteria, extending also to influenza virus (which is not susceptible to ordinary germicides, but is to ultraviolet light). Gaseous glycols are even more effective (O. H. Robertson *et al.*, 1941). Liquid glycol is a relatively feeble germicidal agent, requiring up to 75 per cent. In the form of mist, propylene glycol, 0.2 mg. per liter of air, kills micro-organisms immediately; triethylene glycol is effective as 0.005 mg. per liter of air. Even considerably lower concentrations are claimed to be effective clinically, but this has not been sufficiently controlled for cross infections (Hollaender, 1947). The action probably involves condensation on the bacteria, acting as nuclei. High humidity of the air almost completely inactivates the glycol mist (W. F. Wells and Zappasodi, 1942). The maximal efficiency for triethyleniglycol vapor requires air humidity of 45 to 50 per cent, but substantial effects are obtained at 18 to 32 per cent (M. Hamburger *et al.*, 1945). Propylene glycol mist is harmless in the amounts used (W. Henle and Zellat, 1941). However, *triethylene glycol vapor* is especially effective (1:100,000,000 of air); it is odorless and is claimed to be the least toxic glycol (Robertson *et al.*, 1943). Addition of 1 to 5 per cent to the diet of young rats for two years did not change their growth, but the mortality was greater. Some developed calcium oxalate bladder stones, and the renal tubules sometimes contained oxalate concretions (H. J. Morris *et al.*, 1942).

The general pharmacology of the ethylene glycols was studied by von Oettingen and Jirouch, 1931. They cause local irritation, produce hemolysis, and depress muscular and nervous tissues. The intensity of these actions parallels the surface tension of aqueous solutions, the precipitant action on proteins, and the solution partition-coefficient. The *local irritation* of the undiluted glycols is less than that of 70 per cent alcohol. Propylene glycol is the least irritant (Latven and Molitor, 1939).

The relative toxicity on oral or parenteral administration increases in the sequence: glycerol: propylene glycol: diethylene glycol: ethylene glycol: diethylene glycol monoethyl ether: dioxane: ethylene glycol monoethyl ether (Holck, 1937; Lang *et al.*, 1938). The United States Food and Drug Administration, 1943, classes ethylene glycol, diethylene glycol, polyethylene glycol, and carbitol as definitely toxic. The single dose mortality for rats and guinea pigs has been studied on sixty glycols and derivatives by H. F. Smyth *et al.*, 1941. The *hydropic necrosis* of the renal tubules, and sometimes of the liver parenchyma, is produced only by the compounds that have an ether linkage between the glycol molecules, by diethylene glycol and its methyl, ethyl and butyl esters, by dioxane, and by dipropylene glycol; not by ethylene glycol and its diacetate, though these may cause deposition of oxalate in the kidneys and mild renal insufficiency. Even large intravenous doses of propylene glycol produce only hemoglobinuria and casts (P. J. Hanzlik, Newman *et al.*, 1939; E. P. Lang, Calvery *et al.*, 1939).

Propylene glycol, N.N.R., is used as a solvent and diluent similar to glycerin. It is a viscous fluid, *Sp. G.* about 1.036, miscible with water, alcohol, chloroform and ether. It produces moderate *local irritation* on application to mucous membranes and on hypodermic or intramuscular injection. It is readily *absorbed,* and is oxidized in the body similarly to ethyl alcohol or glycerol, the rate of combustion being largely independent of the dose. A part is excreted unchanged by the urine, to 45 per cent in twenty-four hours, with large doses (A. J. Lehman and Newman, 1937). The rapid combustion and excretion help to explain its low toxicity, which is about the same as for glycerin. Addition of propylene glycol to the *drinking water* of rats, up to 5 per cent, has no effect on normal growth; and even 10 per cent causes only a temporary check. No lesions in the viscera are demonstrable after 100 days (Reid Hunt, 1932; Hanzlik *et al.*, 1933; Holck, 1937; Weatherby and Haag, 1938). When the basal diet of rats includes 30 per cent of propylene glycol, growth and reproduction are somewhat less than with the same percentage of glycerin (Whitlock *et al.*, 1944). The *minimal fatal dose* for oral administration is about 33.5 Gm. per Kg.; hypodermically, 14 Gm. per Kg.; intravenously, 6.8 Gm. per Kg. (Weatherby and Haag, 1938). Large doses are narcotic, its potency (and its toxicity) being about a third of that of ethyl alcohol. Hemoglobinuria does not occur after oral ingestion of 12 cc. per Kg. (Lehman and Newman, 1937).

Ethylene glycol is about twice as toxic as propylene glycol, and about half as toxic as diethylene glycol, but the ratio varies for different animals (Haag and Ambrose, 1937). Added to the drinking water of rats, 3 per cent ethylene glycol proved fatal in an average of eight days, 5 per cent diethylene glycol in about two weeks, 3.6 per cent propylene glycol did not kill in ten weeks (Holck, 1937). Reid Hunt, 1932, considered ethylene glycol as toxic as methyl alcohol, although less dangerous, because it is not as rapidly absorbed. Page, 1930, however, observed no toxic effects in dogs on administering 9 cc. per Kg., as 30 per cent solution; the undiluted caused emesis with 5 cc. per Kg. He swallowed 15 cc. of the 80 per cent glycol without any noticeable effect except a slight feeling of warmth as it was swallowed. Several instances of poisoning by drinking ethylene glycol as antifreeze fluid ("*prestone*") are on record with symptoms of vomiting, somnolence, prostration, stupor and coma. Death may occur in twelve hours by paralysis of respiration; or hemorrhagic nephrosis may set in (J.A.M.A., 1930; *94:* 1940; Hansen, 1930). Hunt attributed the toxicity of ethylene glycol to its *oxidation to oxalic acid;* but it appears that this involves only a small fraction, and can not account for the phenomena. Monoacetate of ethylene glycol also yields a small quantity of oxalic acid; dioxane, diethylether of ethylene glycol and ethanolamine do not (F. H. Wiley *et al.*, 1938).

Ethylene glycol monoethyl ether is used as a solvent, "*cellosolve.*" A single thorough application of a solution containing 40 per cent in dilute alcohol is reported effective against head lice (W. A. Davis, 1943). A case of industrial poisoning with encephalopathy, in which this played a part, was reported by Donley, 1936.

Diethylene glycol obtained much notoriety as the toxic agent of the Massengill "sulfanilamide elixir," which resulted in the death of at least seventy-six and possibly more than a hundred people before its sale could be stopped. The chief effect is a severe chemical nephrosis with an unusual type of intracellular edema of the epithelial cells of the involved tubule, resulting in their destruction by compression.

The clinical symptoms started in twenty-four to forty-eight hours, with nausea, abdominal cramps, dizziness, malaise, vomiting, occasional diarrhea, lumbar pains. The urine diminished, and in fatal cases anuria became complete in two to five days, with rapid rise of blood urea and creatinine. Drowsiness developed, and slight edema, sometimes slight jaundice, then stupor and coma, cyanosis, pulmonary edema, subnormal temperature, and death after two to seven days of anuria and uremic coma. The pathologic changes consist of generalized edema, hydropic degeneration of the renal tubules, peripheral necrosis of the liver, sometimes hemorrhages into the gastro-intestinal tract. Identical visceral changes result from the administration of diethylene glycol to animals (Geiling and Cannon, 1938). The mechanism of the intracellular edema is not known. It may be that the unusual solvent properties break down the osmotic resistance of the cell membrane. *Bladder stones and tumors,* generally fibro papillomas, developed in rats after prolonged feeding with a diet containing 4 per cent of diethylene glycol (A. A. Nelson *et al.*, 1945).

The acute fatal dose of diethylene glycol for rats is 5 cc per Kg. intravenously, 7 cc. intramuscularly and 15 cc. by mouth. Rabbits are killed by about half the dose, also in *subacute* poisoning. The latter is fatal with much smaller doses: rats are killed in two to five days with daily oral administration of 3 to 6 cc. per Kg., with terminal anuria and coma as in man, and with the same pathology. Dogs vomit, so that the dosage becomes indefinite (Haag and Ambrose, 1937; Geiling *et al.*, 1937; Holck, 1937; Lang *et al.*, 1939).

Fate.—About half (40 to 70 per cent) of the orally administered diethylene glycol is excreted unchanged in the urine; only traces escape unabsorbed in the feces. The oxalic acid excretion is not appreciably increased, and is no higher than with glycerol administration (Haag and Ambrose, 1937). It evidently has no part in the toxic effects.

Local Hypersusceptibility.—B. A. Newman, 1938, reported vesicular dermatitis from handling cigarettes moistened with diethylene glycol; and positive patch-test with 5 per cent solution.

Diethylene glycol heated to about 150° C. is a convenient medium for the *sterilization of surgical instruments* (Gurchot and Mellars, 1940), but it is dangerous, since it may flash and burn at 135° C. (L. B. Tuckerman, 1941), although it boils only at about 250° C.

Diethylene glycol monoethyl ether, "carbitol," is about twice as toxic as diethylene glycol in acute poisoning (Geiling and Cannon, 1938). Its local application to the conjunctiva and wounds is less irritating than corresponding concentrations of glycerin (Cranch *et al.*, 1942).

Dioxane, the anhydride of diethylene glycol, produces essentially identical toxic effects. H. Barber, 1934, reported five subacute deaths in factory workers, with uremia, hemorrhagic nephritis, central necrosis of the liver. Similar lesions occur in animals (de Navasquez, 1935). Dogs also show gastro-intestinal disturbance and weakness (Schrenk and Yant, 1936).

Triethylene glycol is considerably less toxic than diethylene glycol, with continued administration (O. G. Fitzhugh and Nelson, 1946).

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DEMULCENTS OR MUCILAGINOUS SUBSTANCES

These comprise gums and other colloid substances, which form viscid solutions with water and are insoluble in alcohol. They are used to emulsify oils; to suspend insoluble powders; to mitigate the taste and local effects and to delay the absorption of other drugs; and to ally inflammations of mucous membranes, especially in bronchitis, gastritis, enteritis and diarrhea. The effects are local, but in the respiratory passages they extend reflexly into the bronchi. Gums and proteins (raw eggs, milk, flour) are employed for their protective action against irritant poisons. They are also precipitant chemic antidotes for metals. Acacia or gelatin is added to saline injections, to prolong their sojourn in the circulation (see Index, "Saline Infusions"). Mucilages and similar drugs (salep, Irish and Iceland moss) were formerly considered carbohydrate nutrients; but it has been shown that they are imperfectly digested, and for the most part eliminated unchanged by the feces (Mendel, 1908; Swartz, 1911). Psyllium is used as a laxative.

Demulcents as Flavors.—Gums and similar substances diminish the characteristic taste of all substances, acid, salt and sweet, as well as bitter. They act by enveloping the substance and forming a protective layer over the mucous membrane, and in this way preventing the access of the substance to the taste organs, and in the case of acid, chiefly by adsorbing this on the colloidal surface in loose combination (Schoene, 1928), so that the taste, for instance, is much less sour. Colloid substances of this kind are present in fruits as pectin bodies, and have a marked influence upon their taste. The raspberry, for instance, actually contains more acid than the current and but little more sugar, its less sour taste being due to the greater amount of these pectin substances present in it.

Gastric mucin itself has been administered as antacid protective against gastric and duodenal ulcer, 2.5 Gm. of a purified preparation (N.N.R.), precipitated by alcohol from digested mucosa of hog stomach, in water every two hours if necessary (Fogelson, 1931, 1936; Ivy and Fauler, 1931). It is disagreeable to take. The "*plant mucin*" of *okra* is more pleasant, but less effective. Fantus advocated *karaya gum*, a teaspoonful of the coarsely granular powder, stirred into water; but several cases of atopic hypersensitivity have occurred, with nasal, bronchial, cutaneous and gastro-intestinal reactions (Figley, 1940). *Pectin* also has a prophylactic and curative effect on gastric ulcers induced by cinchophen (M. Winters *et al.*, 1939).

Anaphylactoid phenomena on intravenous injection of gums are described under Anaphylaxis—see Index.

Starch (Amylum, U.S.P., maize starch) is used as a dusting powder. By boiling with water, starch undergoes hydration and polymerization and becomes a hydrophilic colloid, starch-paste. This is used as an emollient, in the form of *Starch Glycerite*, U.S.P. (10 per cent of starch, 70 per cent of glycerine, 0.2 per cent of benzoic acid); in poultices; and to secure the retention of enemas (teaspoonful, rubbed smooth with a little cold water and poured into a cup of boiling water). It is a chemical antidote to iodine. Boiled starch, which is much more digestible than the raw, is employed as a nutrient, especially as "*arrowroot*," the starch of Maranta, which has a somewhat finer flavor than the official corn starch. *Barley water* is used as a demulcent decoction; and as a protective colloid in diluting cow's milk for infants, to prevent the precipitation of solid masses of casein in the stomach. It is prepared by boiling for twenty minutes ten parts of washed pearl barley with 150 parts of water, and straining.

***Acacia**, U.S.P. (Gum Arabic), is the dried gummy exudation from Acacia Senegal or of other African species of Acacia. It occurs as spheroidal tears, fragments or powder; whitish to light amber colored; nearly inodorous; insipid, mucilaginous taste. Insol. in alcohol and lipid solvents, slowly forms a slightly acid solution in twice its weight of water. Incompatible with strong alcoholic solutions, borax or metallic salts. The *Mucilage of Acacia*, U.S.P., contains 35 per cent acacia, with 0.2 per cent of benzoic acid as preservative. Average dose, 15 cc.

Tragacanth, U.S.P., is a dried gummy exudation from the stems of Astragalus species. Swells in water to a gelatinous mass, without dissolving. Used in pill excipients, emulsions, etc.; 0.5 per cent suspends insoluble powders in water; 2.5 per cent produces a jelly. *Mucilage of Tragacanth*, U.S.P., contains 6 per cent, with 18 per cent of glycerin and 0.2 per cent of benzoic acid.

Methylcellulose forms stable, viscous, colorless, clear solutions with cold water. They have a refractive index similar to the cornea, and appear to be promising as conjunctival demulcent (K. C. Swan, 1945).

Demulcent Teas.—Drugs containing mucilages are used as decoctions, *ad libitum*, mainly in folk medicine. They include Althea (Marshmallow Root), Cetraria (Iceland Moss, a lichen), Chondrus (Irish Moss, Carrageen, a seaweed), Cydonium (Quince Seed), Salep (tubers of an orchid), Sassafras Pith, Sweet Almonds (Amygdala Dulcis) and Ulmus (inner bark of Slippery Elm).

POULTICE MASSES

Poultices (cataplasms) are used to convey heat and to macerate the skin. Hot water bags, radiant heat and diathermy are now preferred for heating, as being less "messy." A variety of pasty materials may be employed. The most common are linseed, starch, bread and clay. *Linseed poultice* is prepared by stirring one part of ground linseed into three parts of boiling water, to which a little baking soda may be added, to render it fluffy and less irritant. *Clay or kaolin poultice* is much heavier, but can be sterilized if desired. The rate of cooling of different poultice masses has been investigated by Pilcher, 1908. They do not differ materially. Immersion in paraffin baths of low melting point may be used as a "*paraffin poultice.*" Whole linseed is made into a demulcent decoction against bronchitis.

INDIFFERENT DUSTING POWDERS—ADSORBENTS

Very fine ("impalpable") insoluble, nonirritant powders, such as talcum, chalk, starch, zinc stearate, lycopodium, etc., are used to cover and protect the skin and mucous membranes, ulcers and wounds. They prevent friction, absorb secretions by capillary action, and are therefore drying. The insoluble bismuth salts also act largely in this manner. The bismuth salts, chalk, kaolin (clay, bole), fuller's earth and charcoal are used internally for similar protective effects, against gastrointestinal irritation. Dusting powders also adsorb dissolved or suspended substances on their large surface, and diminish their concentration in the solution and their absorption. This weakens the action of chemical agents, including bacterial products. At the same time, the drying renders the medium unsuitable for bacterial growth and so diminishes infection. The chemical antiseptic potency of powders is much weaker when these are applied in a thin layer to the skin or mucous surfaces than when they are heaped on, as in the usual plating tests (J. H. Brewer, 1939).

Water-absorbent powders should not be used on extensive profusely secreting raw surfaces, as they tend to cake and form adherent crusts. Starch becomes doughy even from sweating, and requires the addition of an antiseptic (2 to 4 per cent of boric acid or 1 per cent of salicylic acid) to prevent fermentation. *Zinc stearate*, magnesium stearate and lycopodium have a fatty surface which adheres to the skin and is not wetted by water, so that they permit seepage and evaporation, and do not crust (Fantus). They prevent irritation of the skin of infants by urine.—The use of *talcum powder* about open wounds, even for dusting surgeons' gloves, should be avoided. The particles act as foreign bodies, producing tubercles and fibrosis; in the peritoneum they cause adhesions (E. J. McCormick and Ramsey, 1941).

Prepared chalk is less hazardous, but may produce granulomas before it is absorbed. Potassium bitartrate or starch gums may be used (Seeling *et al.*, 1943). *Lycopodium should not be used on wounds.* It consists of the spores of a clubmoss, which may act as foreign bodies to induce indolent chronic inflammatory reactions and granulomas that may necessitate operation (Antopol and Robbins, 1937). It is also likely to be allergic.

Water Absorbing Power.—Sollmann, 1919, found this to range from 70 to 80 per cent for fuller's earth, kaolin and starch; and from 53 to 65 per cent for chalk and talcum.

Adsorption of Toxins and Antitoxins.—Diphtheria toxin and antitoxin are both adsorbed by animal charcoal; not by kaolin, talcum, kieselguhr or wood charcoal. This does not apply to other toxins and antitoxins. Tetanus toxin is absorbed by all the above agents (Zunz, 1913). In general, gram-positive bacteria are adsorbed much more effectively than the gram-negative (Eisenberg, quoted from Clark).

Face Powders.—The application of indifferent powders protects the skin against the irritation of sun and wind. The usual ingredient of the light powders is starch; of the heavy powders, barium sulfate and talcum. Addition of stearates facilitates adhesion to the skin. They are usually indifferent, but they tend to obstruct the ducts of the skin glands, and so may themselves become irritants. Organic powders may be subject to allergy. Some powders contain zinc oxide, bismuth subcarbonate and even lead carbonate. The lead is directly harmful. The presence of aniline dyes and perfumes in powders and other cosmetic preparations is sometimes responsible for severe dermatitis (Cole, 1924; H. E. Miller and Taussig, 1925).

Adsorbents in Diarrhea.—Bolus alba (kaolin), fuller's earth, bone black (carbo animalis), and tripoli (silica) check watery diarrheas and dysentery. In acute bacterial dysentery, large doses are given, 30 to 45 Gm. three times daily, stirred into hot tea (after a preliminary cleansing by calomel). Smaller doses suffice in chronic dysentery (Stumpf, 1914; Stoerk, 1915). The anti-diarrheal effects are explained by the more solid consistence of the stools; by the checking of bacterial growth; and by adsorption of the irritant putrefactive products (Kraus and Barbara, 1915). Excessive and prolonged administration may lead to accumulation of the adsorbent in the intestines (Bungart, 1917), but serious trouble is exceptional.

Kaolin is also used against peptic ulcer. The acidity of the gastric juice forms some aluminum chloride and silicic acid (J. Friedenwald and Morrison, 1937). It has been reported that adsorbents restrain somewhat the activity of digestive ferments (Strauss, 1916; Peterson, 1917); but this is probably unimportant. Gastric carcinoma is reported to have followed long-continued use of a kaolin preparation (A. L. Cohn *et al.*, 1941).

Hydrous magnesium trisilicate is used as antacid and adsorbent in treating gastric hyperacidity and the pain of *peptic ulcer*. Mutch, 1936, finds that the antacid action is sustained for hours and results in the formation of hydrated silica, which is strongly adsorbent for food poisons and other substances, including pepsin, protecting the ulcer against digestion. Even large doses do not disturb gastro-intestinal motility, causing neither constipation nor diarrhea; but the magnesium chloride may be laxative. It can not reduce the reaction of the stomach materially below neutral and does not easily induce systemic alkalinization, as the excess is insoluble and is voided in the stools. The urinary silicate is increased (Page *et al.*, 1941). Hydrated Aluminum Oxide is used similarly (see Index).

Charcoal against Indigestion and Flatulence.—Freshly heated charcoal adsorbs gases. This presumably led to its use against flatulence and heartburn. It is unsuccessful, for charcoal can not adsorb material amounts of free gases when it is moistened.

Wood charcoal, which is generally used, is slightly alkaline. However, it would be a wasteful and inadequate means of introducing alkali, since 1 Gm. neutralizes only about 5.5 cc. of N/10 acid, and is therefore equivalent to about 42 mg. (⅔ grain) of sodium bicarbonate.

Charcoal as Antidote.—Many substances, including alkaloidal salts, are quite effectively adsorbed by charcoal. This may slow their adsorption sufficiently to prevent toxic effects (Wicshowiki). However, only active charcoal (bone black or mineral charcoal) can be successful, and this is not always available (Joachimoglu, 1922).

According to Leschke, 1 Gm. of animal charcoal binds 850 mg. of mercuric chloride, 580 mg. of strychnine, 40 mg. of phenol. The protective adsorption of alkaloids and organic bases was studied by Loffler and Spiro, 1920.

Colloidal carbon (caramel) is harmless, even on intravenous injection. It antagonizes alkaloids (strychnine) when mixed *in vitro*, and even somewhat when the strychnine is given by mouth, and the carbon by vein; but this antagonism is too uncertain for practical application (Sabbatani, 1913 and 1914).

Charcoal is used to *decolorize solutions*. Different specimens vary greatly in activity. Tested by methylene blue, blood charcoal is generally the most active, but mineral charcoal may be more active than blood charcoal. Graphite and lampblack are almost inactive (Koltoff, 1919). Wood charcoal prepared from nut shells is highly active; ordinary wood charcoal is poor. Talcum and kieselguhr are used to *clarify turbid mixtures*.

Selective Adsorption.—The affinity of adsorbents varies for different substances. In general, it is most effective for colloids of the opposite electric charge (Koltoff, 1919).

The adsorption of gases by charcoal increases with the pressure and decreases with the temperature. Gases of high temperature of liquefaction are generally better adsorbed. At 20°, active blood charcoal adsorbs about seven volumes of hydrogen, twenty-five volumes of nitrogen, oxygen or carbon monoxide; forty volumes of methane; eighty-five volumes of carbon dioxide; 200 volumes of ammonia or hydrogen sulfide (quoted from Bancroft).

Protection against Chemical Irritants.—The adsorbent powders protect the respiratory passages and the skin against irritant "gases" (Sollmann, 1919).

Intravenous injection of colloidal powders tends to produce allergic shock. Kaolin is hemolytic when added directly to the blood (Friedberger and Tsumeoka, 1913). Saint-Jacques, 1934, claimed beneficial results in infections from intravenous injection of animal charcoal, 3 cc. of 2 per cent suspension, repeated six times. He attributed the improvement to phagocytosis.

PREPARATIONS.—*Activated Charcoal*, U.S.P. (Carbo Activatus), is the residue from the destructive distillation of various organic materials, treated to increase its adsorptive power. It may be dispensed when "Wood Charcoal" (Carbo Ligni) is prescribed. A black, odorless, tasteless powder; free from gritty particles. Dose, 1 Gm., 15 grains. The dry powder, in a bag of gauze, is used locally as deodorant for fetid ulcers. *Bone Black* (Carbo Animalis) is used against dysentery, in dosage of 30 Gm.

Kaolin (China Clay, Bolus Alba) is a native hydrated aluminum silicate derived from feldspar, powdered and freed from gritty particles by elutriation. It is used externally as a poultice mass (Cataplasma Kaolini).

Bentonite, U.S.P., is a variety of clay, hydrous aluminum silicate, occurring as a very fine, practically colorless powder. It is insoluble in water, but swells to about eight times its volume when added to water, forming a gelatinous mass. Suspensions have a high *p*H, to 10.5, producing alkali by hydrolysis. The water-holding capacity is changed by acids and alkalis. *Bentonite Magma*, U.S.P., is a 5 per cent suspension in water. Bentonite increases the viscosity of suspensions and is used for this purpose in *Chalk Mixture*. *Fuller's Earth* is also a variety of native aluminum silicate. It absorbs grease readily.

Lycopodium, U.S.P., the spores of Lycopodium clavatum, is used as a light, nonadhesive dusting powder.

Magnesium Trisilicate, U.S.P., $2MgO.3SiO_2.nH_2O$, is a tasteless white powder, almost insoluble in water, partly soluble in acids. Dose, 1 to 4 Gm., 15 to 60 grains, before meals. *Magnesium Trisilicate Tablets*, U.S.P., 0.3 and 0.5 Gm.

Talcum, U.S.P., a hydrous magnesium silicate, insol. in water and dilute acids and alkalis, is used for dusting.

Zinc Stearate, U.S.P., is a compound of zinc, corresponding to 14 per cent of ZnO, with varying proportions of stearic and palmitic acids. It is a fine, white, bulky powder, insoluble in water.

MECHANICAL PROTECTIVE AGENTS

Collodion, U.S.P. (Collodium), is a solution of not less than 5 per cent Pyroxylin, U.S.P. (soluble gun cotton, chiefly cellulose tetranitrate), in a mixture of ether and alcohol, 3:1. A clear or slightly opalescent syrupy liquid; colorless or slightly yellowish and having the odor of ether. Highly inflammable; should be kept in a cool place remote from fire. Pyroxylin is also soluble in acetone. Collodion dries rapidly into a firm film, which is used to protect small wounds. The film cracks easily and contracts considerably, exerting pressure on the tissues. Collodion applied over the harvest-mite itch gives prompt relief and kills the parasite (C. D. Fowler, 1944). *Flexible Collodion*, U.S.P., is collodion rendered flexible by castor oil and camphor.

Purified Cotton, U.S.P. (Gossypium Purificatum, Absorbent Cotton), consists of the hairs of the seed of Gossypium herbaceum freed from adhering impurities, deprived of fatty matter (so as to make it absorbent), bleached and sterilized. Almost pure cellulose. It is used in bandaging, as the fiber (Absorbent Cotton), as gauze (Tela, Carbasus), and as lint (Lintum). It may be impregnated with antiseptics or astringents.

Plasters serve for protection against irritation, for mechanical support; and rarely for the slow conveyance of drugs to or through the skin. They are somewhat irritant, partly by preventing evaporation from the skin, and partly by the small quantities of volatile oils contained in the resins from which they are often prepared. *Adhesive Plaster*, U.S.P., is a mixture of rubber, resins, waxes and an absorbent powder (starch, zinc oxide, etc.), spread on cloth.

Adhesive plaster irritation may be minimized by painting the skin with merthiolate solution before the plaster is applied (R. E. Legge, 1941). Previous application of a varnish (Compound Tincture of Benzoin) facilitates removal of the plaster.

Rubber eczema, usually vesicular, occurs in some individuals on prolonged contact with rubber. It is often due to the accelerators and antioxidants used in its manufacture, or to substances formed in the cold-vulcanization with sulfur dichloride. The latter become innocuous on soaking the rubber in 4 per cent sodium hydroxide (Overmayer, 1933). Rubber tubing used for intravenous injection should be thoroughly boiled.

Lead Oleate Plaster (Diachylon Plaster) is a lead soap. *Court Plaster* is made of isinglass (Ichthyocolla), a variety of gelatin prepared from the swimming bladder of the sturgeon.

Plaster of Paris (Calcii Sulfas Exsiccatus, Burnt Gypsum), $CaSO_4 \cdot \frac{1}{2}H_2O$, is made by heating native gypsum, a hydrous calcium sulfate, to 250° to 400° F., with the loss of about ¾ of its water. It forms a fine white powder used in bandaging. Mixed with half its weight of water, it forms a hydrate, which is first colloidal, then crystallizes into microscopic interlacing needles, "setting" into the stony plaster in fifteen to twenty minutes. This may be delayed to an hour by the addition of 5 per cent of glycerin, colloids, gelatin or glue. It may be hastened by the addition of sodium silicate or other sodium or potassium or calcium salts. Plaster of Paris must be kept dry. A mixture with flour 1:2 is used as rat poison (Holsendorf, 1937).

Sodium Silicate is used in bandaging in the form of *Liquor Sodii Silicatis* (*waterglass*) containing about 20 per cent. It is a colorless syrupy liquid, of alkaline properties, but not corrosive, and forms a solid glassy mass on exposure.

Actions of Sodium Silicate.—When given by mouth or skin, this acts like a typical mild alkali without showing any specific features. It is readily absorbed from the alimentary canal, and excreted by the urine. Injected intravenously it causes agglutination of blood corpuscles, and consequently intravascular clotting.

Colloidal Silicic Acid.—Intravenous injection of large doses (150 mg. of SiO_2 per rabbit) produces death within three to five minutes, by intravascular coagulation. With sublethal doses, the coagulation of shed blood is accelerated; but the addition of silicic acid, *in vitro*, does not alter the coagulation time of normal blood. Bronchioconstrictor effects in isolated perfused guinea pig lung have been reported (Filley *et al.*, 1945). With injections of 40 to 60 mg. death occurs after three to five days. The tissues show marked degeneration of the vascular endothelium and focal necrosis of the parenchymal cells, especially in the liver and kidneys. The daily injection of 5 mg. is well tolerated, but in the course of several months it leads to extensive fibrosis, especially in the liver and kidneys (Gye and Purdy, 1922, 1924). Colloidal silicic acid has been tried in tuberculosis, including experimental tuberculosis in guinea pigs, with alleged beneficial effects (Messner, 1922; Kahle, 1921). It failed to establish itself clinically.

Organic Silicates.—*Tetraethyl ortho silicate*, used as solvent in industry, produces toxic effects, chiefly pulmonary capillary hemorrhages, regardless of the method of administration. Surviving animals develop nephritis (Kasper *et al.*, 1938). The toxicity of ethyl silicate has been studied by H. F. Smyth and Seaton, 1940.

Silicosis is an occupational disease, characterized by pulmonary fibrosis, produced by prolonged inhalation of dust rich in silica, such as sandstone, and known as "miners' consumption." The fibrosis is a chronic condition which favors the development of tuberculosis.

Etiology.—Crystallized silica, SiO_2, is present in most mineral dusts, but the pulmonary irritation develops only if the silica content is high, and if the powder is fine, for particles larger than 10 microns do not reach the alveoli (H. B. Wulff, 1934). Colloidal silica is probably the most active, but other silicate dusts also produce the lesions, especially asbestos and talcum. The mechanism is not known, but it seems to involve a special toxicity of the silica, which is appreciably soluble in body fluids. Carborundum dust with particles as sharp and hard as those of silica does not result in comparable lesions (L. U. Gardner, 1923; L. T. Fairhall, review, 1945). More than a million workers in the United States are exposed to silica dust, and a fourth of those exposed acquire some degree of silicosis, but few die of it directly (Proske and Sayers, 1934). About three per cent of the miners who have worked ten years or more become silicotic annually (Watkins and Pitchford, 1927).

Clinical Phenomena.—The onset is slow and insidious. The symptoms consist of shortness of breath, decreased chest expansion, diminished capacity for work, without fever (J. S. Haldane, 1914). The essential *anatomic lesion* is a distinctive type of nodular fibrosis, the "*silicotic nodule*," which has also been produced experimentally in animals by long-repeated inhalation or insufflation of silica, borosilicate glass and quartz. The particles are soon engulfed by macrocytes and moved to the lymphatic tissue, where they cause marked proliferation of the fixed tissue cells. After some months the macrocytes degenerate. The liberated silica is then taken up by other cells and giant cells are formed, the whole enveloped by fibrous tissue, similar to the nodules of tuberculosis (L. U. Gardner, 1937; review, O. H. Robertson, 1941). Many believe that the nodules are really tuberculosis modified by silica irritation. Pure silicosis is rarely of clinical significance. It is nearly always associated with tuberculous infection (review, King and Belt). The effects are likely to progress after the exposure is discontinued, for the deposited silica continues to irritate (review, R. R. Sayers, 1934; W. I. Clark, 1936). Hypodermic injection of finely powdered quartz into the external ear of rabbits provokes inflammation in which the silica particles appear to have toxic effects on the various white cells (Fallon and Banting, 1935).

Aluminum Powder as a Preventive of Silicosis.—J. J. Denny *et al.*, 1939, found that the solubility of silica *in vitro* is almost completely prevented by the addition of small quantities of powdered aluminum. This is converted to the gelatinous aluminum hydroxide, which surrounds the silica particles with an insoluble coating, and adsorbs any that may have been dissolved. They report that inhalation of silica does not produce silicosis in rabbits if 1 per cent of powdered aluminum is added. The aluminum particles should be less than 5 microns in diameter, and free from grease. Prolonged inhalation of 1 per cent aluminum had no bad effects, locally or systemically. E. J. King *et al.*, 1945, found much less favorable results in rats. The aluminum disappeared in time, leaving the quartz, so that the effect would not be permanent. There is some further question whether equal protection would be conferred under the somewhat different conditions of industrial exposure. Control of dust should not be neglected (Report of Councils, 1946, J.A.M.A., *130:*1223).

Occurrence of Silica.—Very small amounts of silicates are normally present in all tissues (Siegfried, 1901). There is no evidence that they play any physiologic role. Silica is also constantly present in hairs and feathers (H. Schulz, 1901). It constitutes up to 77 per cent of the total ash of the feathers of the dove (Gonnermann, 1918).

Silica occurs normally in the urine of man, dogs and cats, and in larger amount in that of herbivorous animals, due largely to the greater intake in their food. In men not exposed to silicosis, the urinary concentration ranges from 0.25 to 2.25 mg. SiO_2 per 100 cc. (L. J. Goldwater, 1936), averaging 16.2 mg. per day, but varying with the diet (Page *et al.*, 1941). If a fine quartz suspension is administered by stomach tube, the urinary excretion is promptly increased, for about six hours. Silicate absorbed from oral administration of silicic acid or sodium silicate (or magnesium trisilicate, Page *et al.*, 1941) passes rapidly into the urine without material increase of the silicate level of the blood. Intravenously injected soluble silica promptly takes the same path (King *et al.*, 1933). *The silicate content of human tissue* normally ranges from 10 to 200 mg. per 100 Gm. of dry weight. The normal content of the human spleen is about 15 mg. per 100 Gm. of dry weight; 140 mg. in normal lung, and $>$ 200 mg. in silicosis lung (E. J. King *et al.*, 1933). Because of the normal inhalation of dust, it is relatively high in the lungs of adults even without silicotic lesions (review, E. J. King and Belt, 1938). It is concentrated especially in the root glands, where the percentage may reach fourteen times that of the parenchyma (Antoine, 1935; King and Belt, 1940). Youngsburg and Youngsburg, 1940, found 0.086 to 1.3 per cent of SiO_2 in the dried lungs of fourteen silicotic patients; 3 to 91 per cent of the total Si existed as free SiO_2. There is no direct correlation between silica concentration and the degree of fibrosis of the lung (King and Belt, 1940). Spectroscopic methods reveal little in human blood, generally less than 0.1 mg. per cent; even exposed workers show little (H. Weil, 1938).

Asbestosis.—Workers exposed to the dust of asbestos (hydrated magnesium silicate) develop pneumoconiosis and pulmonary fibrosis, demonstrable by x-ray shadows, of a somewhat different type than silicosis, with milder symptoms, usually with little disability and with no marked disposition to tuberculosis, pneumonia or other lung infections.

Asbestosis was first described by W. E. Cooke, 1927. The *clinical symptoms* consist of progressive dyspnea, cough, substernal pain, blood-stained sputum, decreased chest expansion, weakness, clubbed fingers; in later stages, cyanosis and distressing dyspnea, paroxymal coughing, tenacious sputum, containing particles of asbestos. Microscopic examination shows a large amount of finely granulated pigment in the peribronchial tissue and alveolar cells (Lanza, 1936; Sayers and Dreessen, 1939). The difference from silicosis is probably due to the larger size of the asbestos dust particles, so that they do not enter the alveoli. Macrophages form giant cells around the asbestos, giving rise to asbestos "bodies." Fibrosis occurs much more slowly (review, O. H. Robertson, 1941).

LOCAL IRRITANTS, CORROSIVES AND ASTRINGENTS

The local actions of drugs are simple and much alike, since they occur ordinarily in only a few situations, especially the skin and mucous membranes. The majority of local poisons produce the typical phenomena of inflammation ("irritation"), by causing injury of protoplasm through coagulation, liquefaction, etc. Many of these reactions can be reproduced in the test tube with proteins, but the extreme sensitiveness of protoplasm to reagents renders almost all substances—even water—irritant under suitable conditions. All irritants are somewhat *antiseptic*, by injuring the protoplasm of the bacteria.

The differences between the various irritants involve chiefly the strength of their action in different situations. Some act especially on the alimentary canal, and to a very small extent on the skin. This is probably connected with differences of absorbability. A drug which can not penetrate the skin does not act upon it. The epidermis is impermeable to many substances. In order to penetrate, the irritants must be either fat-soluble like croton oil or turpentine, or they must actually destroy the epidermis, like caustics. The degree of the local action depends usually upon the *concentration* rather than on the absolute quantity of the irritant. A small quantity of concentrated acid does more damage than much larger quantities diluted.

Degrees of Cutaneous Irritation.—The general phenomena of irritation can be studied typically on the skin. They are identical with the familiar changes produced by scalds or burns of increasing severity. They may be observed by applying the agent to a small piece of filter paper or gauze attached to the skin, the "*patch test*," used especially to study hypersusceptibility to drugs (Schwartz and Peck, 1945), or to a very superficial scratch, as in testing for allergies.

Rubefaction.—The first degree of irritant action consists in arterial and capillary hyperemia, at first active, later passive. This constitutes rubefaction ("dermatitis erythematosa"), and the agents which produce it are called *rubefacients*. The dilatation involves at first the most superficial vessels, but progresses to the deeper subcutaneous structures, partly directly and partly by reflexes. The congestion is accompanied by itching, burning or pain, sometimes succeeded by more or less anesthesia. If the irritant action does not go further, resolution takes place by the return of the vessels to normal, without leaving any lesions. The pain may outlast the congestion. The upper layers of the skin are usually desquamated. If the action is stronger than rubefaction, it may pass into vesication or pustulation.

Inflammatory Edema.—Increased permeability of the vessels is an early phenomenon of acute inflammation. It may result in edema. The *permeability to dissolved substances* is also increased. For instance, when trypan is injected by vein, it appears much more abundantly in the aqueous humor of an inflamed than of a normal eye (P. A. Lewis, 1916).

Urticaria.—Localized edema of the corium is a rather special mild inflammatory reaction to many drugs, particularly in susceptible individuals. It may occur on systemic administration, or more readily by application to the scarified skin. The more important drugs producing this effect are: morphine and its esters; histamine and peptone. Milder grades occur with atropine, cocaine, formaldehyde, urea and many amines (Sollmann and Pilcher, 1917; Sollmann, 1917).

Mechanism of Inflammatory Edema.—Increased capillary filtration in inflammation involves both transient increase of capillary pressure (by local vasodilatation and increased number of functioning capillary channels) and increased permeability of capillary endothelium to fluid and to dissolved substances of large molecules, such as the plasma proteins, trypan blue, graphite particles, india ink, antitoxin, vaccine virus (V. Menkin, review, 1938). If these are injected intravenously in the early stages of inflammation they are deposited in the irritated area (R. H. Rigdon, 1940). Lewis and Grant, 1924, referred the capillary dilatation to a histamine-like substance liberated by the injury. Menkin, 1938, believes that histamine plays only a subsidiary role. He attributes the phenomena to a diffusible polypeptide, "*leukotaxine*," which he has isolated from inflamed tissues. It increases the permeability of small vessels, and is followed by rapid immigration of leukocytes. Neither its chemical nor its pharmacologic properties agree with histamine.

Vesication (blistering) occurs if the exudate is greater than can be carried off by the lymphatics. The liquid accumulates in the parts of the tissues offering the least resistance to distention. In the skin, it penetrates readily through the lower layers of the rete Malpighii, but is arrested by the impermeable stratum corneum. It is therefore confined between the upper and lower layers of the rete and separates them, causing blisters or vesicles. The agents which produce these are called *vesicants* or *epispastics*. The vesicles appear as small points which gradually coalesce into a large blister. The fluid is at first clear, but becomes turbid by leukocytes. The sensory stimulation is stronger than in rubefaction. Resolution takes place without loss of tissue by the formation of a new stratum corneum from the rete. The area may remain pigmented for years. If the overlying and separated layers of epidermis are removed, infection may occur, the lower layers of the rete offering but little resistance. The infection may lead to loss of substance. If the vesicant is allowed to act after the blister has been formed, the infiltration becomes purulent, with deeper destruction of the skin, and healing with scar formation. This degree of action should be avoided.

Pustulation occurs if the irritant does not penetrate the epidermis, but only the cutaneous glands. Discrete and later confluent pustules are formed, which heal with more or less "pitting." They produce severe sensory irritation, but are now rarely used. The principal pustulants are croton oil and tartar emetic.

Aseptic Pus Formation.—A few drugs possess specific chemotactic power on leukocytes; their injection (hypodermic or into serous cavities) leads to pus, even when asepsis is perfect. Turpentine, croton oil, petroleum, mercury, silver nitrate, digitoxin, cadaverine, aleuron suspensions, etc., are the principal examples. The chemotropic response of polymorphonuclear leukocytes involves only the direction, not the speed of their movements (H. M. Dixon and McCutcheon, 1936).

Influence of Systemic and Local Conditions on Cutaneous Irritation.—There are *local differences* in susceptibility, and if an irritative reaction has once been induced, the skin remains hypersensitive for some time. Roentgen ray and radium treatment may leave the skin hypersensitive for months (Mackee and Andrews, 1921). Sunshine and ultraviolet rays sensitize to *tar* irritation (Herzheimer and Nathan, 1917). The *tuberculin reaction* in children is markedly decreased by the local injection of epinephrine or pituitrin for long after the vasoconstrictor effect has subsided. Drugs that cause an urticarial reaction also decrease the tuberculin reaction. It is increased by caffeine. The *Schick test reaction* is increased by epinephrine and pituitrin, decreased by caffeine and by urticarial agents (von Gröer *et al.*, 1929).

Dermatitis from Systemic Drugs.—Many drugs cause *dermatitis* when they are given by mouth (belladonna, arsenic, iodoform, quinine, salicin, antipyretics, iodides and bromides, digitalis, chloroform, etc.). This is sometimes due to changes in the cutaneous circulation, sometimes to the excretion of the drug by the skin, and often to allergic hypersusceptibility. It may take the form of scarlatinal, desquamating urticarial or papular rashes or acne. The more common sources of drug eruption may be grouped as *Erythematous or Polymorphic Eruption:* Antipyrine, arsenic (including arsphenamine), benzoic acid, boric acid, bromides, copaiba, chloral, iodide, morphine, quinine, salicylates. *Scarlatiniform Rashes:* Antipyrine, atropine, benzoate, belladonna, chloral, iodoform, ipecac, mercury, salicylates, sulfonal. *Urticaria:* Benzoate, copaiba, cubebs, iodide, quinine, salicylates, valerian. *Purpura:* Antitoxin, arsenic, barbiturates, chloral, copaiba, cubebs, iodide, mercury, quinine, sulfonal. *Morbilliform Eruptions:* Antipyrine, antitoxin, belladonna, copaiba, cubebs, mercury, opium.

Occupational dermatoses constitute two-thirds of all cases of occupational disease in the United States, and most of these are due to chemicals and plants, the most common being petroleum products and greases (12 per cent of all occupational dermatoses); plants (11 per cent); alkalis (10 per cent); solvents (9 per cent); metals and plating (8 per cent). Hypersensitivity is a frequent cause; cleanliness is protective; oily skins are more resistant than are dry, Negroes and brunettes more than blondes (review, L. Schwartz, 1939). Solvents act largely by removing the fat from the skin, leading to dryness and fissures (S. M. Peck, 1944). Skin hazards in the production of synthetic rubber are discussed by L. Schwartz, 1945; fabric finishes by Schwartz, Spolyar *et al.*, 1940. Paraphenylenediamine, methanamine and other amines, phenols, coal tars, dyes, photographic developers and terpenes used in perfumes, cosmetics and wearing apparel (Schwartz and Peck, 1945) frequently cause dermatoses. Dermatosis has been reported from the rind of citrus fruit dyed with "yellow O.B." (ortho toluene-agobetanaphthylamine) (Traub, Gordon and Van Dyke, 1937), and from lipstick containing methyl heptine carbonate (H. L. Baer, 1935). *The methods of studying irritation and toxicity on local application* are discussed by Draize, Nelson and Calvery, 1944. *Patch tests for susceptibility to contact dermatitis in industry* should be used routinely, especially for new chemicals and new personnel. The U. S. Public Health Service classifies cutaneous irritants as (1) *primary*, with direct action on normal skin; and (2) *sensitizers*, which cause a specific change of susceptibility, so that dermatitis develops after five or more days by further contact at the same or other location. These allergic reactions tend to increase for a day or two after the patch is removed, while primary irritation generally decreases. An agent may produce both primary irritation and sensitization (L. Schwartz and Peck, 1945). The anaphylactic sensitization by simple chemical substances is attributed to formation of antigenic compounds with tissue proteins. Sometimes this may be initiated by a nonspecific irritant; for instance, picric acid does not produce sensitization if it is applied to the normal skin of guinea pigs, but does so if the skin is first irritated with cantharidin (Landsteiner and Di Somma, 1940). *Hyposensitization* ("hardening") develops with most primary irritants on repeated exposure. *The technic and interpretation of patch testing* are explained by L. Schwartz, 1944.

Corrosion, cauterization or direct destruction of tissue occurs if the agent (cauterizant or escharotic) acts chemically on the protoplasm, as do strong acids or alkalis, iodine or bromine, some metallic salts, etc. This leads to the production of a scab or "eschar," and resolution by scar formation. The chemical destruction of tissue is generally preceded by inflammatory necrosis. Chemical cauterization therefore shows three areas: the first, situated at the depth and periphery of the ulcer, is an area of simple inflammation and hyperemia. Then follows a layer of necrotic tissue, the result of the inflammatory action; and last, a layer in which the chemical cauterization results in solution of the cells which have already been killed by the inflammatory process. These three—hyperemia, inflammatory necrosis and chemical solution—are successive stages in the same action; and by proper dilution, the second or first degree of action may be obtained without the succeeding stages. The *eschar* (scab) is formed by coagulation of the inflammatory exudate and by chemical products (albuminates, etc.) of the interaction of the corrosive agent with this exudate and with the killed cells. If the proteins are dissolved (as by alkalis), the scab is soft; if they are precipitated (as by most metals), it is hard. If the scab is soft, the corrosive agent penetrates it and spreads and extends deeply, so that the alkalis are not manageable for cauterization. If the scab is solid, it prevents deeper penetration, and the action can be confined to the desired areas.

Malignant tumors may be induced by prolonged exposure to a variety of irritant agents, such as radium, x-ray, ultraviolet radiation, polycyclic hydrocarbons, sex hormones, tumor extract, "butter yellow" dye, arsenic and viruses. The disposition varies for different agents, and the susceptibility differs greatly with individuals, chiefly by their genetic constitution, so that animal experiments should be made on pure-bred strains (fifteen generations of inbreeding in mice: C. L. Little, 1937).

Astringent Action.—Agents which are strongly precipitant produce relatively mild irritation; and if their concentration is not too high, their primary inflammatory effect does not proceed to necrosis; on the contrary, it leads to diminution of any existing inflammatory process. This "astringent" (drawing together) action is characterized by visible contraction of the tissue; blanching and wrinkling of mucous membranes; and diminished exudation, or secretion of mucus, according to the place of application. These agents also possess a peculiar "astringent" taste. The effects are probably due to precipitation and hardening of the cell surface and cement substance of the capillary endothelium, producing contraction and decreasing the permeability of the capillaries; and thus counteracting the essential phenomena of inflammation (congestion and exudation). Astringents are *used therapeutically* to check diarrhea, reduce inflammation of mucous membranes, promote healing, and to arrest hemorrhage (by coagulating the blood). They should not be employed in the early stages of bacterial invasion, when the inflammatory reaction is needed for defense. The *principal astringents* are: metallic salts, tannins, dilute acids and strongly hypertonic solutions.

Quantitative Estimation of Astringent Action.—This has been measured by Motolese, 1910, by noting the degree in which the extensibility of frogs' lungs is reduced after immersion in the astringent solution (Dreser's method). With 1 per cent solutions, the order was: silver nitrate > tannin > lead subacetate > picric acid > lead acetate > alum > zinc sulfate. Astringency may also be studied by the suppression of mucus secretion from the frogs' skin (Schuetz), and more simply by the tanning of blood corpuscles or even by quantitative precipitation of proteins (Sollmann, 1920). Heubner and Schreiber, 1937, describe the microscopic changes as seen by darkfield illumination.

Astringent Effects Are Strictly Local.—Since astringents are precipitated by proteins, they can not be absorbed or exist in the blood or tissues in effective form. Before this was understood astringent action throughout the body was attempted by external application or by giving astringents by mouth.

Astringents on Peristalsis.—In the *intestinal canal* the astringents form a deposit along the lumen of the intestine, and diminish absorption, the penetration of other irritant substances and peristalsis.

Irritation of Mucous Membrane.—Differences in detail are seen when irritants are applied to the mucous membranes. There is less tendency to vesication, since the epithelium is not impermeable. The oral mucous membrane presents a transition; it blisters, but less readily than the skin. Pustulation can not occur since this depends upon the cutaneous glands. The mucous glands are stimulated to increased activity, producing "*catarrhal*" conditions.

Gastro-Enteritis.—The actions of irritants on the alimentary tract present special features; the effects being stomachic, carminative, nauseant or emetic; diarrhea, dysentery; abortion; corrosion and perforation; according to the nature and degree of their action.

Respiratory Passages.—If an irritant poison is *volatile*, its main effects may be upon the *respiratory passages*. The general phenomena are those of acute laryngitis, bronchitis or pneumonitis. Similar effects follow the aspiration of nonvolatile irritants.

Local Irritation of Wounds and Ulcers.—The effects are usually more marked than on the intact skin. Even the milder irritants destroy the superficial cells, especially if diseased; but the deeper cells multiply more rapidly, partly through direct stimulation and partly through the hyperemia. Mild irritants therefore *promote healing.* Astringents, balsams, quinine, salts and even water have this therapeutic action.

Hypodermic injection of irritants produces more or less pain, and often aseptic abscesses or fibrosis. The danger of infection is considerable if the tissues are killed by the irritant. With intramuscular injection, the pain is less severe.

Irritant Effects after Absorption.—Many irritants are not absorbed; and even when absorption occurs they are too greatly diluted to have much effect, except at the place of their absorption and excretion; *i. e.*, the liver and kidneys. Other tissues are involved only if the administration is long continued, as in alcohol or lead poisoning. These may lead to increase of connective tissue, arteriosclerosis, hepatic cirrhosis, etc.

Drug nephritis is produced by all absorbable irritants and often occurs acutely. The inflammation may involve all the renal tissues, or it may be predominantly glomerular or parenchymatous, according to the poison. Continued administration leads to interstitial nephritis.

Phenomena.—The inflammation is characterized by albuminuria, casts and the histologic lesions. The urine flow is increased in the early stages, and decreased later (Schlayer and Hedinger, 1907). The excretory efficiency is diminished (Eisenbrey, 1911, 1913). The changes in nitrogen and chloride excretions are complex. The nitrogen excretion is decreased in tubular nephritis (uranium), not in glomerular (arsenic). Retention of nitrogen in the blood occurs especially in tubular nephritis (Foster, 1915). Renal glycosuria may occur (E. Franck, 1913; Pollak, 1911); also hepatic edema (Opie, 1912), and sometimes slight myocardial changes (Walker, 1911). Hemorrhagic nephritis is seen with cantharides, turpentine, formaldehyde, etc. Edema occurs only with uranium, at least in animals. The restoration of the blood volume afert saline injections is delayed in uranium. chromate and tartrate nephritis (Bogart. Underhill & Mendel, 1916)

Tubular nephritis with little or no primary glomerular injury is produced by uranium, chromate, mercuric chloride and aloin. The anatomic changes in the early stages of *uranium* and *chromate* nephritis are confined essentially to the tubules, especially the proximal convoluted, and consist of granular and fatty degeneration and necrosis. *Mercury* acts similarly, but mainly on the ascending loops of Henle, with deposition of lime salts. This occurs also with uranium and chromate, but to less degree (J. P. Simonds and Hepler, 1945). The glomeruli are at first unaffected, but later show thickening of the capillary walls, and vascular disturbances can be shown by physiologic methods

Glomerular nephritis, generally with some secondary involvement of the tubules, is produced by arsenic, cantharides and snake venom. Diphtheria toxin acts on all the structures; and many other irritants act diffusely. The anatomic changes vary according to the poisons. *Arsenic* produces little or no anatomic change, except dilatation of the capillary tufts, filling Bowman's capsules. Physiologic methods, however, show serious vascular injury. The *cantharides* changes involve both the glomerular tufts and space. The capsules are filled with desquamated cells, whose origin is disputed. There is also functional vascular injury. The functional changes are not proportional to the anatomic.

Chronic nephritis is difficult to produce experimentally, the acute experimental lesions usually ending in rapid and complete recovery. Positive results have been obtained by Ophuls with lead, by Dickson with uranium, and by Klotz, 1914, with infections.

Aging Process and Tissue Resistance.—Recovery from hepatotoxic agents, such as uranium, mercuric salts and chloroform, is effected by regeneration of less specialized but more resistant cells. This regeneration is less effective in senile than in young animals (review, MacNider, 1942).

Reflex Effects of Irritants.—Stimulation of sensory areas acts reflexly on the vasomotor, cardiac, respiratory and other centers, producing changes in the circulation, respiration and other functions. These vary with the place, extent, speed, intensity and kind of stimulation, and with the state of the centers. They are used in therapeutics, especially for "counterirritation."

Consciousness may be restored by counterirritation, in fainting, light coma and narcosis. The usual measures for this purpose are dashing with cold water, slapping with wet towels, or inhalation of dilute ammonia vapor (smelling salts or aromatic ammonia).

The Respiratory Reflexes.—If the respiratory center is depressed, as in collapse, morphine poisoning, anesthesia, asphyxia, etc., moderate counterirritation produces marked stimulation; and if the collapse is not too deep, natural respiration may be restored (Meissner, 1923). *If the respiration is normal,* mild cutaneous irritation may either slow or quicken the rate. If the irritation is strong, the respiration is always slowed. Sudden and extensive stimulation, as by cold douches, produces momentary standstill, followed by deep inspirations. Continued painful stimulation causes deeper and often faster breathing Hanzlik, 1923, utilized the respiratory response as an index of local irritation.

Circulation.—Local irritation gives rise to augmentatory and inhibitory vasomotor and cardiac reflexes. Heat causes general vasodilatation of the skin, while cold results in constriction. *Mild tactile stimulation* (for instance, blowing on the skin) also tends to produce widespread vasoconstriction and therefore some rise of blood pressure (Gruetzner and Heidenhain, 1877). Reflex vasoconstriction involves mainly the cutaneous vessels, except those which are dilated by direct contact with the irritant. The renal vessels are also constricted, while those of the brain are dilated (Wertheimer; Roy and Sherrington). The heart rate is quickened (Naumann). The tactile and auditory constrictor reflex occurs only if the brain is intact, *i. e.*, it requires psychic stimulation; the heat and cold reflexes persist after decerebration. *Stimulation of sensory nerves, if weak or slow, i. e.,* of the kind to evoke reflexes of the voluntary muscles, tends to produce vasodilatation and fall of blood pressure, seen most typically with the depressor nerve. It involves inhibition of the vasoconstrictor tone, stimulation of the vasodilator innervation, and stimulation of the cardiac inhibitory center (Bayliss, 1908). *Strong stimulation of sensory nerves* produces vasoconstriction and rise of blood pressure, increasing with the intensity of the stimulation, which must be twenty to 200 times that which suffices for the depressor response (Stiles and Martin, 1915). This is also the primary response of *pain.*

Reflex Shock.—If strong stimulation is prolonged, especially if the subject is conscious, the rise of pressure is followed by fall of blood pressure and internal temperature, especially if there is violent pain, in connection with extensive corrosion. Different mechanisms may be concerned. The heart may go into fibrillation by disturbance of conduction, the response of the vasomotor centers may be inverted by the psychic impulses or by exhaustion, and in corrosion, toxic shock may develop by the absorption of the proteolytic products.

Hypodermic Injection of Mild Irritants.—The injection of ether, camphor, whisky or oil of turpentine generally produces a slight and transient rise of blood pressure; the effect differing quantitatively according to the site of the injection, being, for instance, greatest from the nasal septum. It fails when the vasomotor center is depressed, as in deep anesthesia, shock or hemorrhage (Lieb and Herrick, 1917).

Gastro-Intestinal Irritation.—Sollmann, Brown and Williams (1907) showed that irritation of the stomach or peritoneum has practically no early effect on the blood pressure in anesthetized animals, even when the anesthesia is light. There is generally a marked increase of respiration, and sometimes a slight and momentary rise of blood pressure, but no fall is noticed for several hours. This holds true both for mild irritants, such as peppermint, mustard or moderate heat, and for strong corrosion by formaldehyde, concentrated acids or actual cautery, even when these measures produce perforation. *Irritation of the mouth and larynx* produces very much more marked effects (Sollmann); even contact with 5 per cent acetic acid causes struggling, convulsive rise of blood pressure and dyspneic respiration.

Volatile Irritants on Blood Pressure.—The vapors of strong smelling substances, when applied to the nose of rabbits, raise the blood pressure; but lower it when applied to the trachea. Both effects are reflex (Yamada, 1920).

Carotid Sinus Reflexes.—Various drugs provoke respiratory, circulatory or other reflexes on contact with the chemical receptors of the carotid glomus, but their action is by specific stimulation, not by general irritation (C. Heymans *et al.*, 1932; Comroe and Schmidt, 1937).

Renal Reflexes.—Heat (diathermy), cold, and cutaneous irritants (mustard, capsicum, cantharides, ultraviolet erythema) applied to the lumbar dorsal region cause reflex diuresis, which may be prevented by cocainization of the area, or by removal of the kidney on that side (Brings and Molitor, 1932). Irritation of the urinary bladder by irrigation with 7.5 per cent resorcin or 2.5 per cent collargol, or by overdistention with water, retards renal secretion. This is prevented by anesthetizing the bladder with procaine (Bebeshina and Konradi, 1934).

Counterirritation.—Irritation of the skin may relieve inflammation in deeper seated structures, diminishing the pain and probably the congestion, and perhaps leading to an earlier and more conservative termination.

This treatment by "counterirritation" was employed more extensively by the older physicians, who imagined that the dilatation of the skin vessels would draw the blood out of the neighboring vessels, and so "deplete" the congested area by a direct "derivative action." This crude mechanical conception had to be abandoned as the anatomy and physiology of the circulation became better known. The fact of such "action at a distance," however, may be definitely shown: Cold applied to one hand constricts the vessels of both hands, and heat dilates them (G. N. Stewart, 1913), while irritation of the hand by mustard does not increase the local blood flow, as might be expected from the rubefaction (Wood and Weisman, 1912; Hewlett, 1913); nor is the skin temperature increased by mustard or turpentine rubefaction (N. B Taylor, 1923).

The effects of counterirritation are due mainly to nervous reflexes, partly sensory and partly vascular. The sensory vasomotor reflexes which have been described, like reflexes in general, exhibit the predilection for the homologous nerve paths, *i. e.,* a quantitative localization of the response to definite areas. They are the reversal of the "referred pain," which occurs in definite skin areas when the corresponding viscera are irritated (Head). This explains the empirical observation that counterirritation is most effective when applied at a definite place for each internal inflammation.

The relief of pain by counterirritation is explained partly by homologous reflexes, and partly by the diversion of the attention of the patient from the disease pain, to the usually more bearable sensations of the counterirritant.

Influence of Pain on Inflammation.—According to some observers, the response to chemical inflammation may be diminished or abolished by local anesthesia or central analgesia. Others have failed to find anything more than the normal individual variation.

Bruce, 1913, reported that mustard oil failed to produce conjunctival congestion and edema (chemosis), if the sensory fibers were degenerated, or paralyzed by local anesthetics. The observations were confirmed by Januschke and Bardy, 1914, who also claimed that the inflammation was prevented by nicotine, and that therefore the phenomena involved the sympathetic synapse. Others, however, believed that spinal reflexes were involved, especially as central analgesics, such as ether and morphine, were also said to be effective. Similar results were claimed for calcium chloride, antipyrine, quinine, salicylates, cinchophen, bromides, etc., and substances yielding available oxygen (Amberg, Loevenhart and McClure, 1917). On the other hand, H. H. Stevenson and Reid, 1915, reported that neither nerve degeneration nor local anesthesia influenced the ordinary course of mustard oil chemosis. Morphine and chloral tended to prevent the edema, but only in toxic doses, and presumably as a result of the circulatory collapse. They call attention to the fact that patients with degenerated nerves, with hysteria and with central anesthesia all react to cantharidin vesication. Hanzlik *et al.* showed that paraphenylenediamine edema is not influenced by the analgesics and anesthetics, but only by agents that markedly restrict the local circulation.

Changes in the Blood.—Irritation of the skin produces changes in the blood which may influence inflammation: Winternitz, 1896, found at first *leukopenia*, then *leukocytosis*. Van den Velden, 1912, claims that the coagulability of the systemic blood is increased by a number of local irritant and especially vasoconstrictor processes (ice to the skin; astringents or epinephrine to the mouth; cocaine to the nose; turpentine inhalation, etc.).

Therapeutic Indications of Cutaneous Irritation.—This is employed mainly in the following conditions: (1) *In certain skin diseases*, for the local effects—alkalis, sulfur, chrysarobin, etc. (2) *To promote diaphoresis*—alcohol, friction, heat, etc. (3) *For reflex stimulation of the central nervous system*, in fainting, collapse, narcotic poisoning, accidents of anesthesia, etc.—ammonia inhalation, heat or cold. (4) *To alter the distribution of blood*, to prevent colds—mustard; to relieve congestion of viscera—poultices, vesication; or to promote the absorption of exudates—iodine, vesication. Counterirritation is, as a rule, useful only in chronic inflammation. In acute inflammation there is danger of increasing the process or of causing it to extend to neighboring organs. (5) *To diminish pain*, especially in neuralgic and rheumatic affections—turpentine and other volatile oils, capsicum, chloroform. (6) *As a general tonic*, in the form of salt-water baths or alcohol frictions.

Therapeutics of Cauterization.—Cauterization is sometimes employed for severe *counterirritation*, but particularly to *remove tissue:* (1) In cases of poisoning, snake bite, etc.; (2) for the removal of pathologic tissue, tumors, warts, etc.; (3) indolent granulations, etc.; (4) to cause cicatricial contraction of hypertrophied mucous membranes (nose, etc.); (5) for removing the nerves of teeth; and (6) to remove superfluous hair. In many cases chemical cautery has been replaced by galvano- and thermocautery, which are more prompt and permit a more exact limitation of the cauterized area. On the other hand, the slower effect of chemical caustics is of advantage in permitting a graduation in the strength of the action, or in confining it to certain tissue elements. Pathologic formations, with poor blood supply, are in this way more profoundly altered than normal tissue. The caustics may be applied in solid form (sticks, or fused at the end of a probe), in paste or in solution—the first being the most strictly localizable, the last the most diffuse. In the latter case, or when the tissue liquefies, the surrounding skin should be protected by petrolatum.

GENERAL TOXICOLOGY OF IRRITANTS

The phenomena produced by irritant poisons depend on the part of the body with which they are brought into immediate contact. The most prominent symptoms arise from the skin, alimentary canal or respiratory organs; the last only in the case of volatile poisons. Later symptoms may appear in the urinary organs. The extent of the action depends on the concentration of the poisons, the time during which they act, and the extent of surface with which they come into contact—less upon their absolute amount. If taken by the alimentary canal, their action is modified by the presence of food.

Cauterization of the skin may be accidental or criminal. In the latter case it is often by sulfuric acid ("vitriol"). The *results* are the same as in extensive burns. The *diagnosis* usually offers little difficulty. The character of the stains is that described in the next section. Enough of the corrosive can generally be collected from the clothing, etc., to establish its identity by chemic means. The *treatment* is like that for burns, after previous neutralization and removal of the corrosive agent. Salves and oils are useful.

Caustics in the eye are best washed away by liberal application of water. Attempts to neutralize acids or alkalis generally increase the injury (Cosgrove and Hubbard, 1928).

Irritant Poisons in the Alimentary Canal.—The phenomena differ according to whether the irritant produces actual cauterization—a destruction or solution of the tissues—or only inflammation.

Irritants which Do Not Destroy the Tissue.—To this class belong elaterium, croton oil and most other organic irritants, such as volatile oils, formaldehyde, etc. The symptoms are those of a violent *gastro-enteritis:* nausea, vomiting and diarrhea. If the poison acts only when dissolved, and is insoluble in the stomach, as is croton oil, the nausea and vomiting may not be present, only the diarrhea. The symptoms appear correspondingly late. The abdomen is usually distended and painful, especially on pressure. There is extensive dilatation of the splanchnic vessels and withdrawal of blood from other parts of the body. This produces marked changes in the circulation. The pulse is soft, small and quick. The *lowered circulation* reacts upon other organs, and most conspicuously upon the *central nervous system.* There is great anxiety, vertigo, delirium, convulsions, then *collapse,* and finally coma and death. This picture is common to the entire series of irritant poisons. All the abdominal organs partake in the hyperemia, although they do not come into direct contact with the irritant. The organic irritants, especially oil of savin, of tansy and of pennyroyal, have been used to procure criminal *abortion.* The ecbolic effect is secondary to the gastro-enteritis, which is often fatal without accomplishing the object for which it was produced. *Postmortem appearances* consist in intense congestion of the entire alimentary canal, often with inflammatory exudate into the lumen of the intestine. The congestion may be so violent as to produce ecchymoses. If these are present, the vomit and stools are tinged with blood during life. Destruction of tissue is rare. It may occur from gangrene due to the interference with the circulation.

Fixed Caustics.—The most important are the mineral acids; oxalic acid, which, however, stands apart on account of its specific toxic action; other organic acids, the alkalis and their carbonates; the haloid substances, bromine, chlorine and iodine. Phenol and the metallic salts are also to some extent corrosive, but not usually enough to produce perforation. The alkalis and bromine produce the most extensive destruction of tissue, because of their deep penetration. With them, the scar formation is also the most extensive. *Corrosive effects* occur especially in those situations which are in prolonged contact with the caustic: the lips; mouth and pharynx; esophagus at its beginning and end, and where it crosses the left bronchus; and the stomach, especially the pyloric end (because the caustic follows the lesser curvature and accumulates at the pylorus). The firm closure of the pylorus furnishes more or less protection to the intestines. The *appearance of the corrosions and stains* is of diagnostic importance, since they may be recognized about the mouth during life: Alkalis cause transparent swelling of the epithelium, which may detach as a gelatinous mass, exposing the scarlet-colored inflamed area beneath. The other corrosives, which precipitate proteins, produce at first a grayish-white opaque stain. This persists in the case of the metallic poisons. The acids change the hemoglobin in the neighboring area into the dark acid hematin, and the color of the stain consequently becomes dark or black. Nitric acid is an exception: its stain takes on a yellow color. This differs from that of picric acid by being changed to orange by alkalis, while the picric acid stain remains unaltered. Bromine produces a light brown or orange stain; iodine stains a mahogany color. The silver stain turns black after a time.

The symptoms of corrosive poisoning begin in the mouth, with burning pain, dysphagia and loss of tissue. The *taste* of many of the substances is characteristic—acid, alkaline, metallic, astringent, etc. The further symptoms are those of gastro-enteritis, similar to those described under noncorrosive irritants, but generally more severe. The vomiting and diarrhea are more frequently bloody. In the case of acids the vomited blood is darkened by acid hematin, the so-called "coffee-grounds" vomit. The pain is much more marked with corrosive poisons. The destruction of the tissue gives rise to reflexes which may take the form of "shock." The absorption of the chemic products of corrosion may produce fever; or the temperature may be lowered by collapse. If perforation occurs, the clinical picture turns into that of peritonitis. *Death* may occur from shock before the local symptoms have time to develop, it may follow after one or two days of more gradual collapse, or it may result later from peritonitis; or finally, after recovery from the acute effects, the formation of *scar tissue* in the corroded areas may lead to stenosis and thus to gradual starvation. *Postmortem examination* shows stains and corrosions in the mouth, esophagus, stomach and duodenum; with the metallic corrosives, the cecum and large intestines may exhibit the principal changes, since many metals are excreted in these situations. When the action has not progressed to actual corrosion, there is often marked hyperemia and ecchymosis. The color may be much darker than corresponds to the amount of congestion, especially in the case of acids (due to acid hematin).

Treatment of Poisoning by Corrosives.—The first measure is *dilution*, drinking of water and washing out the stomach. If corrosion is already advanced, it is not advisable to pass a stomach tube. The further treatment consists in the administration of *demulcent* substances, such as mucilage or boiled starch, white of egg or milk. Proteins are useful against the metallic poisons, since they form rather insoluble albuminates. The pain may require *narcotics* in free doses. Most of the irritant poisons can be treated by *chemic antidotes; alkalis*, by acids (vinegar, lemon juice or any acid diluted to 1 to 5 per cent); *acids*, by noncorrosive alkalis, preferably magnesium oxide. The free alkalis are usually too caustic, and the carbonates involve danger of rupturing the corroded stomach by the evolution of carbon dioxide gas. Potassium compounds are objectionable because of the danger of toxic absorption from the corroded mucosae. In case of necessity any alkali may be used, such as whitewash or chalk. *Iodine, chlorine or bromine* may be neutralized by sodium bicarbonate.

After the immediate emergency, the esophagus and stomach should be rested to prevent stricture by scarring, and to avoid bacterial decomposition. Instead of drinking water, 5 per cent dextrose should be administered by rectum. Oral feeding should be restricted to olive oil, a teaspoon to a tablespoonful at intervals to a total of 200 cc. per day. This is also protective. Other feeding should not be begun until healing has started, as judged by the visible mucosae, and it should remain soft and liquid till healing is completed (Leschke).

FIXED ALKALIS

These include sodium and potassium hydroxide, which corrode even the skin; quicklime, which because of its limited solubility is caustic only when used in substance; the carbonates of sodium and potassium, which are not caustic, but produce inflammation and necrosis; and the mildly alkaline salts, such as the bicarbonates, borates and basic phosphates, which merely soften the epithelium. The free alkalis combine with the tissue elements to form alkaline albuminates, or with the fats to form soaps, and in this way destroy the substance. They are also hygroscopic, and withdraw water from the cells, which contributes to the necrosis. They gelatinize the tissues. The scab which they produce is soft, and the compounds they form are soluble; consequently the alkalis penetrate deeply, are very painful, and their action continues for several days and leads to extensive scar formation. It is therefore difficult to circumscribe their effects.

This is only partly remedied by mixing them with the nondiffusible quicklime as in the "*Vienna Paste*," a mixture of equal parts of KOH and CaO, stirred into a thick paste with alcohol. Chemical "*hair straighteners*" consist generally of sodium hydroxide (about 6 per cent), which may cause severe burns if it remains on the skin (F. Lewis, 1939).

Poisoning by caustic alkalis (*lyes*) is common. Half an ounce of potassium carbonate would generally be fatal. Sodium carbonate is less toxic. On account of the deep action, *stricture of the esophagus* is a frequent sequel, and the fatality is fairly high. The *treatment* consists in dilution with large quantities of water, to which vinegar, lemon juice or other dilute acid should be added. This should be followed by a tumbler of olive oil or other salad oil. The further treatment is described under Corrosive Poisoning.

Cement burns are caused by quicklime. The immediate treatment is washing with water. They form tough scabs adhering firmly to the underlying tissue, with necrosis progressing underneath. A soothing ointment should be applied for twenty-four hours to loosen the scab, leaving a clean ulcer. Petrolatum may be used for prophylaxis (Meherin and Schomaker, 1939).

Dilute alkalis on the skin soften the epidermis and hair, and emulsify and dissolve fats. They are employed in skin diseases (seborrhea, acne, ichthyosis, psoriasis and epidermal proliferations); to facilitate the penetration of antiseptic remedies into the skin (in scabies, favus, ringworm); to emulsify cutaneous remedies (mercury, tar, sulfur); as lubricants for liniments (soap liniment); as cleansing agents (detergents), especially in the form of soaps and borax; and as depilatories (especially the sulfides). Application of sodium bicarbonate deodorizes hyperidrosis (J. H. Lamb, 1946).

Alkaline baths, used in skin diseases, are best administered at bedtime; sodium carbonate or bicarbonate, potassium carbonate, or borax, in the proportion of about 100 Gm. per bath; for lotions, 2 per cent. *The internal actions and uses* are discussed in another section (see Index).

The "actual" or immediately effective alkalinity of a solution depends on the dissociated OH ions; but as these combine with the tissues, further OH ions are split off ("potential" alkalinity), which continue the action. The total effect, therefore, depends upon the total quantity of OH ions which can be split off under the conditions of the body (Dreser, 1910).

PREPARATIONS.—*Potassium Hydroxide*, U.S.P. (Caustic Potash), KOH, and *Sodium Hydroxide*, U.S.P. (Caustic Soda), NaOH, occur as white masses or pencils, very soluble in water and in alc. They are used as caustics, to remove warts, etc., and to soften epidermis (2 per cent). *Monohydrated Sodium Carbonate*, U.S.P., $Na_2CO_3.H_2O$, is freely sol. in water (1:3) and glycerin, insol. in alc. Used as lotion (0.5 per cent). Dose, 0.25 Gm., 4 grains, diluted. *Washing Soda* contains 10 molecules of water and is about half as strong as the monohydrated. *Potassium Carbonate*, U.S.P. (Salt of Tartar), K_2CO_3, is also very sol. in water and practically insol. in alc. Dose, 0.12 to 1 Gm., 2 to 15 grains, diluted.

Lime Solution, U.S.P. (Liquor Calci Hydroxidi; Lime Water), is a saturated solution (about 0.14 per cent) of *Calcium Hydroxide* (Slaked Lime, $Ca(OH)_2$) prepared from Calcium Oxide. A clear, colorless, odorless liquid, of alkaline taste; *incompatible* with carbonates and "hard" water. Used as antacid, against diarrhea, and externally against burns. It is often added to milk (1:4). Dose, 15 cc. (to 120 cc.), 4 drachms (to 4 ounces). *Lime Liniment* (*Carron Oil*) is an emulsion of equal volumes of lime water and linseed oil. Applied to burns, on cloths, frequently removed. *Unslaked lime* (Quicklime, CaO) is used for disinfecting excreta, adding enough so that the mixture boils; or, less effectively, by slaking the lime with four parts of water, adding this to the excrement in equal volume, and letting stand for two hours before disposal. *Whitewashing* with lime disinfects walls.

AMMONIA

This differs from other alkalis by its volatility. It passes through the stratum corneum of the epidermis and, acting upon the lower layers of the skin, may produce blisters. It is sometimes used for this purpose instead of cantharides, especially in nephritis, where the latter can not be employed. It is, however, more painful. It is used in more dilute form as liniment for counterirritation. *The inhalation of ammonia*, free, or in the form of the aromatic spirit, or of carbonate, is used for reflex stimulation in fainting, etc. Care must be used, since too high concentrations of the vapor may produce bronchitis or pneumonia. For man, it becomes insupportable in the concentration of 1:1000.

Poisoning by swallowing ammonia presents the same phenomena as other caustic alkalis except that the respiratory passages are more involved by the inhalation of the vapor. Five to 10 Gm. of the official solution would be toxic; 30 Gm. is generally fatal, although recovery has occurred from 60 Gm. The *treatment* is the same as for fixed alkalis.

Ammonia burns of the eye should be washed, and the anterior chamber should then be drained by paracentesis, or the absorbed ammonia may destroy the vitreous humor and retina, causing permanent blindness.

For *Preparations*, see Index.

SOAPS

These are alkali salts of fatty acids which dissociate readily so that they act both as mild, noncorrosive alkalis and as fatty acids. Their actions are due chiefly to their high surface affinity and to the formation of tough surface films, by which they emulsify fats. They are therefore detergent. They tend to sterilize the skin by the mechanical removal of bacteria. They also alter the protective surface membranes of the bacteria, but are unreliable as direct germicides. They irritate wounds and so actually increase infection; green potash soap more than white (L. W. Peterson, 1945). Their efficiency is not materially increased by incorporating other antiseptics (Morton and Klauder, 1944). Red blood cells are hemolyzed. The lubricant properties of soap are utilized in liniments that are applied by friction. Soap may be used in skin diseases, similarly to the alkaline salts. On mucous membranes and exposed surfaces, soap is markedly irritant. It is emetic if swallowed. In the rectum, soap secures prompt evacuation. It is used for this purpose as warm soapsuds enemas; or solid, formed into a suppository. Sodium morrhuate is used as a sclerosing agent, especially for varicose veins. *Triethanolamine* combines with fatty acids to form soaps of high emulsifying power. In the newer detergents the fats are replaced by sulfonation products or sulfates of fatty oils, acids or alcohols.

Detergents are classed as (1) *anionic*, soaps, R—COONa; alkylsulfates, R—OSO$_3$Na; (2) *cationic*, substituted ammonium salts, $R_4{\equiv}N$—Cl; (3) *nonionic*, condensed glycol esters ("Medical Uses of Soap," symposium edited by Morris Fishbein, 1945, Lippincott).

Soaps appear to have been used by the Gauls and Germans before they were employed by the Romans and Greeks. They were known, however, when Pompeii was destroyed in 79 A.D.

The detergent action of soaps is due to the mechanical effect of the foam, the emulsification of the grease, and the softening of the epidermis, so that the superficial layers are readily removed with the adherent dirt.

Cleansing creams remove most easily what is soluble in the external phase of their emulsion.

Antiseptic Action.—Strong soap solutions are fairly antiseptic. Even weak solutions are rapidly fatal to *Treponema pallidum* (Reasoner, 1917). J. W. Walker, 1931, found soaps not germicidal for staphylococci or typhoid and spore-forming organisms, but markedly so against the organisms of respiratory infections, gonococci, streptococci, pneumococci, meningococci, diphtheria and influenza. Hot water (35° C.) nearly doubled the potency. J. F. Norton, 1920, found that ordinary soaps remove bacteria from the hands more effectively than the special antiseptic soaps, and pointed out that the addition of germicides would not be effective under practical conditions. White soap and ether are the least injurious *detergents for burns and wounds.* Tincture of soft soap, 95 per cent alcohol, and hydrogen peroxide solution produce superficial necrosis of the cells. Tannic acid and silver nitrate cause deeper necrosis (Z. Baker, 1944). *Phagocytosis* is stimulated by soaps, even in fairly high concentrations; but excessively strong solutions are detrimental (Hamburger and de Haan, 1913).

Intra-uterine injection of soap has been used to induce abortion, but is dangerous. Severe and sometimes fatal effects have been described; profound hemolysis, pulmonary embolism, generalized septicemia, local inflammation and its sequels, total occlusion, peritonitis, circumscribed necrosis of uterine tissue, severe and continued bleeding (Tilcher, 1932).

The chemistry of soaps is not fully understood. The molecules of all active detergents contain both hydrophilic and lipophilic radicles which cooperate in emulsification. The *lipophilic radicle* is a hydrocarbon. The hydrophilic radicle of soap is COONa; in the sulfates the COO is replaced by OSO$_3$; in the sulfonates by SO$_3$ (Land and Black, 1942). The sodium soaps are generally solid, potassium soaps gelatinous. Both form clear solutions with alcohol and more or less turbid colloidal solutions with water. Water hydrolyzes part of the soap into alkali (NaOH) and "acid soap," the latter in colloidal solution or suspension. Its nature is not quite clear, but it is probably chiefly of the pattern NaHR$_2$. The "acid soap" remains suspended as an electro-negative colloid (Diasio, 1934). The degree of hydrolysis increases with dilution and depends also on other conditions. It does not exceed 6 per cent, even with laurate, the most dissociable soap. In alcoholic solutions it exists chiefly as unhydrolyzed electrolyte. Because of the limited hydrolysis, the alkalinity of soap solutions is quite low, generally about $\frac{1}{1000}$ N (corresponds to 5 per cent of hydrolysis in a 1 per cent soap solution); never above $\frac{3}{100}$ N. Higher alkalinity would be due to free alkali (Beedle and Bolan, 1921). Soaps with the largest carbon chains are the most hydrolyzed or alkaline. The alkalinity is decreased by moderate amount of sodium salts, and by lowering the temperature (review, L. D. Edwards, 1939). The concentration of soap in thick lather is about 8 per cent; in dishwashing and laundry solutions it is about 0.3 to 1 per cent.

The hemolytic action of soaps reaches a maximum at a certain *p*H, generally near to neutrality, which is characteristic for each fatty acid, and decreases on the acid and especially on the alkaline side. It is therefore not due to the alkali, but to the fatty acid molecule, acting presumably as acid-soap. This is quite different from *foaming*, which increases with alkalinity; and as foaming is due to decreased surface tension, this must be due to neutral soap. At the optimal *p*H, the hemolytic potency of the soaps decreases in the *sequence* of laurate, myristate, palmitate and stearate; but at their natural *p*H, the hemolysis increases with the length of the carbon chain of saturated fatty acids. Unsaturated acids are more hemolytic, proportional to the number of double bonds. Potassium and sodium soaps have similar hemolytic values (L. D. Edwards, 1939; Buckendahl, 1933; Hettche, 1934). Erythrocyte destruction *in vivo* is increased by the intravenous injection of even very small quantities of soap or fatty acid (5 mg. per Kg.). It is estimated from this that the food fat is responsible for one-twelfth to one-third of the daily erythrocyte destruction (Freeman *et al.*, 1944). *Arbacia ova* are cytolysed by soap solutions between *p*H 6 and 9; the maximum being toward the alkaline end for oleate and linoleate, toward the acid end for ricinoleate (I. H. Page *et al.*, 1932). *The toxicity for earthworms* decreases in the direction of laurate, myristate, oleate, ricinoleate, palmitate, stearate (Edwards, 1939). *Blood coagulation* is prevented by the addition of small quantities of soaps, 3 mg. of sodium stearate or 10 mg. of sodium oleate per liter of blood diluted to two-thirds. Calcium does not inhibit the effect, although it is slightly weakened (Rabbino, 1927). The proteolytic action of trypsin is inhibited by small amounts of soap (R. L. Peck, 1942).

Skin irritation (eczema) by soap appears to be less common than is ordinarily supposed. Even patch tests with .1 per cent solution gave only 14 per cent of positive reactions, and these generally mild. They depended on the added antiseptics and on the nature of the fatty acid, the alkalinity playing a minor role. Ordinary household soaps were found no more alkaline than the best toilet soaps (Beedle and Bolam, 1921). Even "laundry" soaps are probably no more irritating, except by the prolonged contact. "Superfatting" of soaps has no advantage (Land and Blank, 1942). Workers in soap industries do not commonly develop dermatitis.

The percentage of positive reactions was inverse to the molecular weight of the saturated fatty acids. Oleate ranked with saturated acids of high molecular weight. Coconut oil soap (which gives a stiff lather) had a somewhat higher percentage. Hypersensitivity to soap is usually acquired. Newborn infants react less frequently than older infants and children. Patients with contact dermatitis and with allergies react more frequently (J. W. Jordan *et al.*, 1936; I. H. Blank, 1939). With prolonged application of 0.0225 N solutions, B. E. Emery and Edward, 1940, found that soaps from oils containing lauric and myristic acid are the most irritant; but castor oil soap was also relatively irritant. Potassium soaps are generally more irritant than sodium soaps. Sodium alkyl sulfites are less irritant than the Na or K salts of the fatty acids; lauryl and myristicyl are also the most irritant of this series.

Soaps and Other Dental Detergents.—The effects on the ciliary activity of the epithelium of frogs' esophagus were studied by R. L. Perrine *et al.*, 1939, as an index of protoplasmic and epithelial injury. Hard soaps and sodium alkyl sulfates averaged about ten times more toxic than perborate or borate, but various soaps differ considerably. Aromatic oils and camphor in saturated water solution have little effect.

"Soapless soaps" consist of sodium or triethanolamine, $N(C_2H_4OH)_3$, salts of sulfated or sulfonated alkyl derivatives of higher alcohols from fatty acids; for instance, $R.C.O.SO_3Na$ (sulfated) or $R.C.SO_3Na$ (sulfonated), with various modifications. The sulfates are made by heating the oil with sulfuric acid at about 50° C.; higher temperatures produce the sulfonates. They were introduced as detergents by W. Schrau, 1931. They lower surface tension in much greater dilution than do ordinary soaps. They have a neutral reaction, do not turn rancid on standing, and do not precipitate with the calcium and magnesium of "hard" water. They are used for laundry, shampoo and dentrifices (sodium laurylsulfate and sulfacetate; Epstein *et al.*, 1939). They foam so freely that they are employed in about a tenth of the customary concentration of soap. "*Turkey red oil*" consists of ammonium salts of sulfated castor oil. They are also employed to aid absorption through the skin and as thrombotic agents for varicose veins. Some carry positive and others negative electric charges. Higher germicidal potency is claimed for the cationic detergents (Baker *et al.*, 1941). They are less irritant than soap to the skin (Emery and Edwards, 1940), but more irritant to mucous membranes (and also to ciliated epithelium) in equal concentrations, but less so in the lower concentrations in which they are used. As powders they are highly irritant. Hypodermic and intramuscular injections even of 1 cc. of 0.01 per cent of sodium laurylsulfate ("Duponal") produces local necrosis. Intravenous injection causes fall of blood pressure and depression of respiration (Macht, 1944). Continued ingestion of large doses of laurylsulfate by rats is more toxic than ordinary soap, resulting in degenerative changes in the intestinal mucosa, liver, and kidneys (Hatton *et al.*, 1940). They have been used, however, in the treatment of gastric ulcer, since relatively high dilutions denature pepsin *in vivo* and *in vitro*. Doses of 0.2 Gm. every two hours were administered without toxic symptoms, and with symptomatic relief in two-thirds of the patients (Fogelson and Shoh, 1944; Kirsner and Spitzer, 1944).

PREPARATIONS.—***Hard Soap,** U.S.P. (Sapo Durus), is a soda soap; occurs as a solid; slowly sol. in water and alc. ***Medicinal Soft Soap,** U.S.P. (Sapo Mollis Medicatus, *Green Soap*), is a potassium soap made from vegetable oils without removal of the glycerin. It occurs as a translucent, yellowish, unctuous mass. *Liniment of Soft Soap,* U.S.P. (Tincture of Green Soap), is a 2:1 solution of soft soap in alcohol, perfumed with lavender oil. Since the soap does not hydrolyze in alcohol, it is a less effective detergent than water solutions. *Camphor and Soap Liniment,* U.S.P. (Soap Liniment; Opodeldoc), is a solution of hard soap (6 per cent), camphor (4.5 per cent), and rosemary oil (1 per cent) in 65 per cent alcohol.

Sodium Laurylsulfate, U.S.P., is a mixture of normal sodium alkyl sulfates, chiefly sodium laurylsulfate. It is soluble in water (1:10), forming an opalescent solution.—*Triethanolamine,* U.S.P., $N(C_2H_4OH)_3$ (with some mono and diethanolamines in the technical grades usually employed) combines with fatty acids to form nearly neutral detergent soaps which are soluble in water, alcohol, fatty oils and lipoid solvents, only slightly in petroleum oils. It is used in ointments as an emulsifying agent. *Benzylam Chloride,* U.S.P. (*Zephiran Chloride*), is a mixture of alkyl benzylammonium chlorides, which lowers surface tension and acts as detergent similar to soap. It is used as a disinfectant. Its toxicity is low, but it is irritant in concentrations above 1 per cent.

SODIUM MORRHUATE AND OTHER SCLEROSING SOLUTIONS

The sodium soap of the unsaturated fatty acids of cod liver oil is used to destroy the endothelium and to set up localized sclerosing inflammation for the obliteration of varicose veins, by injecting these with a 5 per cent solution of soap, containing also 2 or 3 per cent of benzyl alcohol as local anesthetic. Other irritant agents are used for the same purpose. The solutions are also employed for the obliteration of vascular birthmarks (Kaessler, 1938), and for closing the hernial canal The latter procedure is often ineffective, generally dangerous, and should be restricted to special indications.

Varicose Vein Injection by Sodium Morrhuate.—A 5 per cent solution, with 2 per cent of benzyl alcohol, is marketed in ampuls of 2 and 5 cc. The first injection should be 0.5 cc. of 5 per cent solution, to test for hypersusceptibility. If no bad consequences ensue in twenty-four hours, further injections may be made, usually of 1 cc. and not more than 2 cc. at one site. The total amount injected at a sitting should not exceed 2 to 5 cc., the injections being repeated at intervals of three to seven days. The veins begin to harden in a few minutes and become firm within twenty-four hours. The leg is then firmly bandaged. The sclerosis usually extends 2 to 4 inches below the site of injection. Toxic effects are rare, but collapse has been reported (M. L. Dale, 1937). The injection is usually painless if benzyl alcohol is added; otherwise there may be muscular cramps. Painful infiltration about the vein may last for seven to ten days. Extravasation must be avoided, but does not usually cause gangrene (T. T. Higgins and Kittel, 1930; R. A. Cutting, 1926; F. L. Smith, 1932; W. Cooper, 1933). Solutions stronger than 5 per cent should not be employed; 10 per cent has caused suppurative phlebitis and fatalities.

Other solutions employed for sclerosing veins by the same technic are: dextrose, 50 per cent; dextrose, 25 per cent, with sodium chloride, 15 per cent; invert sugar, 60 and 75 per cent; quinine dihydrochloride, 13 per cent, with urethane, 6.5 per cent; also ethyl alcohol, sodium iodide, iron salts, mercuric chloride, sodium citrate, quinine and urea hydrochloride, sodium salicylate, which is said to be very painful. Dextrose and invert sugar are least liable to produce sloughing if they escape from the vein. *Invert sugar solution* is marketed in ampuls of 6 Gm. and 7.5 Gm. in 10 cc., injecting 5 to 20 cc. of the solution. *Experimental investigations* on dogs with twenty-nine sclerosing solutions gave the most effective thrombus formation with sodium morrhuate. Destruction of the venous endothelium is the chief factor in the production of the thrombus (A. Ochsner and Mahorner, 1934). *In perfused vessels* (rabbit's ear and frog's leg) very dilute solution of soap (1:11,000 in Ringer's solution) causes intense vasoconstriction, not inhibited by atropine, but prevented by the serum colloids, and by *p*H below 6 (W. Ludwig, 1927).

The injection treatment of hernia consists in the production of fibrosis by repeated local injections of sclerosing solutions, which should be "tissue stimulating" but not irritating. Soap solutions appear best; powerful sclerosing solutions, such as are used in varicose veins, should be avoided. The treatment should be employed by only those who have special experience and realize the dangers. These are diminished by careful selection of cases and skillful technic. The treatment is not simple, and requires detailed care for considerable periods, averaging twelve to sixteen injections and check-ups during five months. The results are generally inferior to those of operation; under the best conditions only 57 per cent were "cured" and 15 per cent failed completely. It should be limited to small, recent, indirect hernias of young persons, and to reducible inguinal hernia of children. The complications are transient swelling and hydrocele of the cord, and epididymitis. Intraperitoneal injection is fairly common (5 per cent) and causes shock, which is generally transient, but may be fatal. Subsequent surgery is not materially complicated (F. J. Harris and White, 1938, 1936; C. J. Berne, 1938; C. O. Rice, 1935; Council on Pharmacy and Chemistry Report, 1940, J.A.M.A., *115*:533).

Sodium Morrhuate Injection, U.S.P., a sterile watery solution; usual sizes, 5 per cent in 2, 5 and 30 cc.

ALKALINE SULFIDES AND POLYSULFIDES

When applied to the *skin*, the sulfides (K, Na, Ca) soften the stratum corneum, much like the alkalis. Their action on hair is even greater, so that they are employed as depilatories, especially calx sulfurata and barium sulfide. When taken by *mouth*, they act as irritants and corrosives, through the liberation of hydrogen sulfide and free alkali.

Therapeutic Uses and Preparations.—The sulfides are used externally, in skin diseases (psoriasis, acne, seborrhea), especially as "Vleminckx's lotion," *Solution of Sulfurated Lime*, N.F., a solution of calcium polysulfides and thiosulfate, generally diluted with nine parts of water, and sponged on the surface once or twice daily or as a bath, 2 drachms per gallon. Diluted with an equal volume of water, it is used against scabies. Pusey, 1920, recommends it against warts. These are covered with a dressing soaked in the undiluted solution, applied every night until irritation is produced; then less frequently till the wart disappears or can be removed.

"White Lotion" (*Lotio Alba*), N.F., a freshly prepared suspension of zinc sulfide and sulfur, resulting from the mixture of zinc sulfate and sulfurated potash (4 per cent of each in distilled water), is also used in acne and seborrhea.

Sulfurated Potash, U.S.P. (Liver of Sulfur), is a mixture composed chiefly of potassium polysulfides and potassium thiosulfate; freely sol. in water (1:2); is used in baths (30 to 200 Gm., 1 to 6 ounces, per bath).

Sulfurated lime is a mixture containing about 55 per cent of CaS. A pale gray or yellowish powder; odor of hydrogen sulfide; nauseous alkaline taste; slightly sol. in cold water. Used as depilatory, mixed with an equal quantity of starch and made into a paste. Internally, it is used against boils and other suppurations. Its efficiency is doubtful. *Dose*, 15 to 60 mg., ¼ to 1 grain.

Toxic doses of sulfides produce the systemic effects of hydrogen sulfide. Death has occurred from 12 to 15 Gm. Smaller doses have little systemic action, as they are rapidly oxidized. They are *excreted* in the urine mainly as sulfates; but there seem to be also some organic sulfur compounds. A small amount of some volatile sulfur compound is also excreted by the *lungs*, giving the peculiar H_2S odor of the breath, and causing some *expectorant action*. With *intravenous injection* part is excreted as hydrogen sulfide and part is oxidized to sulfate (W. Denis and Reed, 1927).

Ammonium hydrogen sulfide is a severe skin irritant, penetrates the skin more rapidly than hydrogen sulfide, and may be fatal (Land and Draize, 1942). Ammonium sulfide, $(NH_4)_2S$, when applied to the head in "permanent wave" solutions, has caused acute death (Bunce *et al.*, 1941).

The systemic effects of intravenous injections (2 mg. per Kg. for dogs) consist in brief but intense stimulation of respiration, rise of blood pressure, slowing of the heart and violent convulsions, followed by depression of the medullary centers. The respiratory and circulatory effects have been interpreted as chiefly reflexes from the carotid sinus (C. Heymans *et al.*, 1932, 1933; Winder and Winder, 1933); but Koppanyi and Linegar, 1942, brought evidence that the pressor action is peripheral, so that the respiratory stimulation occurs also after excision of the carotid bodies. Direct application of sodium sulfide to the floor of the fourth ventricle also stimulates respiration (Owen and Gesell, 1931).

HYDROGEN SULFIDE

This gas (H_2S) occurs in sewer gas, in chemical industries and laboratories. It acts as local irritant, partly through its *acidity*, partly by forming sodium sulfide on contact with moist tissue. Even high dilutions produce conjunctivitis and roughening of the *cornea* with gray pinpoint stippling of its outer margin, and keratitis with blebs and ulcers, but these generally recover on treatment (Sjörgren, 1939). More concentrated gas, especially with prolonged exposure, causes pulmonary irritation and pulmonary edema. In acute poisoning, violent systemic effects predominate. They consist mainly in stimulation of the respiration and spinal convulsive centers; and with higher concentrations, in direct paralysis of the respiratory center. Hydrogen sulfide is much more toxic than is commonly realized. It approaches hydrocyanic acid in toxicity and rapidity of action.

Occurrence.—Hydrogen sulfide is formed in putrefaction, particularly of sewerage. "Sewer gas" consists essentially of CO_2, NH_3, CH_4, and 2 to 8 per cent of H_2S Small quantities are also formed in intestinal putrefaction, giving rise to diarrhea and possibly to some of the symptoms of "intestinal autointoxication." Operatives in artificial silk factories are subject to ophthalmic irritation, which is attributed to H_2S; but it has been suggested that the irritation may be due to other gaseous by-products (Bakker, 1924). It is *absorbed through the skin*, sufficiently to produce toxic effects on prolonged exposure to high concentrations (Schütze, 1927). *Prophylaxis* is secured by adequate ventilation, and by the wearing of masks and goggles. The odor of the gas is characteristic, but is about as strong with nearly harmless concentrations as with those that would be immediately fatal. Indeed, high concentrations promptly paralyze the olfactory nerves so that the danger may not be perceived (A. W. Freireich, 1946). Hydrogen sulfide is readily detected in air by blackening lead or silver paper. In case of death, it may be recognized by the blackening of a silver coin laid on the skin.

Treatment of Acute Poisoning.—Artificial respiration (by Schaefer's prone method) promises success if started while the heart is still beating. It may be aided by the inhalation of oxygen containing 5 per cent of carbon dioxide, during and for a short time after artificial respiration (Y. Henderson and Haggard, 1922).

Symptomatology in Relation to the Concentration of H_2S.—Dilutions of 1:200,000 cause definite symptoms. With dogs, 1:10,000 for some hours produces irritation of the conjunctiva and bronchial mucosa. With 2 to 3 parts per 10,000 an hour's exposure is followed by these local irritations, and more prolonged exposure may cause slight systemic symptoms resembling asphyxia, *i. e.*, hyperpnea, nausea, giddiness, headache, cerebral excitement and finally narcosis; 1:15,000 produces death within an hour under coma, often with convulsions; with 1:1000, these phenomena lead to death by apnea in fifteen to thirty minutes. With 1:500 death occurs almost immediately through paralysis of the respiration (Lehmann, 1892; Haggard, 1925). In case of survival, *recovery* occurs promptly; but *pulmonary edema and pneumonia* are liable to follow prolonged exposure to nonfatal concentrations, since the relatively low solubility of H_2S causes it to penetrate the alveoli before it is bound. Severe cases therefore have a bad prognosis. The acute action is chiefly on the *respiration.* Violent hyperpnea occurs with 1:1500, and is followed by acapnia and apnea. With 1:500, the respiration is paralyzed almost immediately. The action is due chiefly to irritation of the carotid sinus, as explained under sulfide. Muscular symptoms, jactitation, rigidity and convulsions are due chiefly to asphyxia. Marked slowing of the *heart*, profuse salivation and cold perspiration may occur with concentrations too small to produce other acute systemic effects. Aside from the occasional slowing, the heart is little affected and may beat strongly for several minutes after the respiration has stopped (Haggard).

Chronic Poisoning.—Repeated prolonged exposure to dilute concentrations produces local irritation of the eyes and respiratory tract, rhinitis, bronchitis, severe conjunctivitis with photophobia and corneal opacity, stomatitis, pharyngitis, digestive disturbances, headache, lassitude, skin eruptions.

Fate.—Hydrogen sulfide is readily absorbed from the lungs and the alimentary canal. It exists in the blood partly free, and partly as sulfides. It is excreted as H_2S by the lungs, and as sulfides by the urine. It is rapidly oxidized into nontoxic products (sulfate, etc.). "*Sulfur bacteria*" oxidize hydrogen sulfide to sulfur as a source of energy (Winogradsky, 1887).

Sulfhemoglobin.—This characteristic hemoglobin derivative, with maximal absorption at wavelength 620, is formed *in vitro* by a two stage reaction involving hydrogen peroxide: $HbO_2 + H_2S = Hb + S + H_2O_2 = HbS +$ unknown products. Reduced hemoglobin does not react with sulfide unless a peroxide is added. The reaction is catalyzed by phenylhydrazine and paraminophenol, presumably by their forming peroxide. The reaction is irreversible. Sulfhemoglobin contains one atom of S for each atom of Fe. Its iron is ferrous, but can be oxidized to ferric by ferricyanide, analogous to methemoglobin. Its properties are similar to those of hemoglobin, except that it does not bind oxygen; but with carbon monoxide it forms a loose and reversible compound (H. O. Michel, 1938; Barkan and Walker, 1942). Sulfhemoglobin appears brown in thick layers and dirty green in thin strata. It is responsible for the *discoloration of cadavers.* It is not formed in life by the administration of sulfides, and is therefore not responsible for the asphyxial symptoms, although the apnea lowers the oxygen saturation (Haggard, 1921; Wolynski, 1932). It may be formed in rabbits by continued ingestion of sulfur (Hijmans van den Bergh and Engelkes, 1922). *Clinical sulfhemoglobinemia* occurs with the administration of acetanilid, sulfanilamide and other benzene derivatives, presumably by the catalytic action mentioned above. It also occurs spontaneously (references in Haggard).

Sulfur Springs.—Hydrogen sulfide is contained in small quantity (ordinarily 1:300,000 to 100,000; but up to 1:4000 in volcanic waters) in a number of mineral waters (sulfur springs) which are used against a variety of obscure disorders—rheumatism, gout, diabetes, etc. When these waters are administered for some time, they cause diuresis and diaphoresis, irritation of the urinary passages, intestinal irritation and muscular pains. Their therapeutic effects are probably due to their laxative, diuretic and diaphoretic actions, although the general hygienic conditions must contribute largely to the results, as with other mineral waters (Boecker, 1895).

SULFUR

Sulfur is employed as a parasiticide in itch; as a mild cutaneous irritant in skin diseases (sulfur ointment); and internally as a laxative for softening the stools, especially for patients with hemorrhoids. It may be mixed with an equal amount of potassium bitartrate. Intramuscular injections of oil solutions of sulfur are used to produce fever for "nonspecific therapy." Colloidal sulfur is injected intravenously or intramuscularly in arthritis, but its usefulness is doubtful.

Manner of Action.—Sulfur itself is inactive, but contact with proteins and alkalis converts it slowly into the active sulfides. This process is so gradual that the action is mild and protracted, unless the finely divided "precipitated" or colloidal sulfur is used. Ordinary or "washed" sulfur therefore deserves preference. Sulfur is somewhat soluble in ointment bases, and this facilitates its action (Sabbatani, 1913). Sulfur is burned for fumigation, the disinfectant action being due to the sulfur dioxide.

The formation of sulfides is effected on the skin by the cutaneous secretions. No change occurs in the stomach; but a considerable amount (to 10 per cent) is converted into H_2S in the intestine, as may be judged from the increased secretion of sulfate by the urine (Denis and Reed, 1927), which is much greater and more prompt with colloidal than with powdered sulfur (Greengard and Wolley, 1940). This change was formerly referred to the alkalis of the intestine; but Heffter (1904) pointed out that the alkali exists as bicarbonate, which can not affect the conversion. He showed that it is produced by proteins of all kinds even after these are boiled. Hydrogen sulfide is formed most abundantly in the large intestines (Taegen, 1912).

Skin Diseases.—Sulfur Ointment, U.S.P., is used for acne and seborrhea; 5 per cent ointment is applied to ulcers to hasten keratinization; 2 to 4 per cent is employed in alopecia; 10 to 25 per cent in petrolatum for scabies. Colloidal sulfur may be used, but in lower dosage (H. E. Miller, 1935).

Alopecia.—Sulfur (2 to 4 per cent) is used in the seborrheic form, as are also other irritants (salicylic acid, 1 to 2 per cent); mercuric chloride, 0.1 to 0.4 per cent; betanaphthol, 1 to 2 per cent; pilocarpine, 0.15 per cent; cantharides; resorcin (1 to 2 per cent; discolors the hair). These agents may be dissolved in water, glycerin or oils, or applied as ointments (Dore, 1914).

Scabies.—The itch mites and their ova are destroyed by the application of ointments containing sulfur (10 to 25 per cent) or betanaphthol (10 per cent) or by balsam of Peru. As the parasites are accessible only when they come to the surface at night, the ointments should be applied in the evening, alternating with scrubbing of the skin and a film of oil. The itching is relieved with the first application, so that this is almost a therapeutic test; but several treatments should be given (J. H. Stokes, 1936).

Nutrition of Chicks.—Sulfur is commonly fed to control coccidiosis. When such chicks are kept away from sunlight they require four times as much vitamin D as those without sulfur. Sunlight prevents this deficiency. The requirements for carotene and riboflavin are not increased (Sherwood *et al.*, 1943).

Colloidal Sulfur in Chronic Arthritis.—Intramuscular and especially intravenous injections of colloidal sulfur solution were reported to give temporary symptomatic relief and often induce febrile reactions which may serve as "nonspecific fever therapy"; but the reactions are uncertain and it can not be predicted whether they will be useful or harmful. The contraindications are practically unknown and the optimal dosage has not been determined. It is no longer employed in the leading arthritis clinics of the United States (report, Council on Pharmacy and Chemistry, 1933, J.A.M.A., *111:*1657).

Colloidal sulfur injections were introduced about 1907 against various diseases, including tuberculosis and syphilis, but were soon dropped, except for arthritis, for which they had been recommended by Cawadias, 1917, who claimed rapid cessation of pain, correction of the deformities and restoration of function. Others obtained variable results, about like those of nonspecific protein therapy (Pemberton, 1930). Recent writers incline to consider the improvement as imaginary. The dosage is 10 to 30 mg. twice weekly. Intramuscular injections sometimes cause extensive necrosis. Advanced age, feebleness, organic disease and obesity are cited as contraindications.

The *effects of intravenous colloidal sulfur* are physical and chemical. Both vary with the degree of dispersion, which is always more or less mixed, depending on the method of preparation and age of the solution (the preparation is described by Luman, 1917). Commercial colloidal sulfur preparations always contain enough sulfide to produce acute rise of blood pressure and respiratory stimulation (Koppanyi and Linegar, 1942). The colloidal suspension tends to produce *anaphylactoid shock reactions*, as such, or after flocculation (this may protect against true anaphylaxis; Montagnini, 1927). The *acute toxicity* depends chiefly on this factor, which varies with the dispersion, the alkalinity of the solution, and the rate of injection (Chistoni, 1933; Wheeldon and Main, 1933).

Fate of Colloidal Sulfur.—With oral administration to man or rabbits, colloidal sulfur is absorbed promptly and almost completely as sulfide, oxidized and excreted as sulfate in the urine, within twenty-four hours. Massive doses administered to rabbits by stomach tube produce toxic sulfide effects in a few minutes (Greengard and Wolley, 1939). Attempts have been made to explain the supposed effects of sulfur in arthritis on the basis of disturbances in sulfur metabolism which were supposed to exist in this disease, such as deficiency of chondroitin sulfuric acid in the cartilage (Meyer-Bisch *et al.*, 1921). Other workers, however, have failed to find these changes or effects (H. A. Reimann and Pucher, 1924; Cawadias, 1925). Freyberg *et al.*, 1939, confirmed that the administration of colloidal sulfur by any method, or of thiosulfate, does not significantly increase the conjugated sulfate, either in normal subjects or in rheumatoid arthritis; nor does it increase the cystine content (in fingernails)

Intramuscular Injections of Sulfurated Oil.—One to 2 cc. of olive or other oils boiled with 0.1 to 2 per cent of sulfur cause local reaction with considerable pain, leukocytosis and fever of about 102° F., beginning in about seven hours and lasting about fifty hours. It was originally tried in paralytic dementia (K. Schroder, 1929), but the results were not good (McCartan, 1932). It was then used for chronic infections, rheumatism and arthritis with variable results, similarly to milk injections. The latter deserve preference, as they are quite as effective and their local effects are less severe (L. M. Waller and Allen, 1931; T. D. Power, 1932).

PREPARATIONS.—*Sublimed Sulfur,* U.S.P. (Sulfur Sublimatum; Flowers of Sulfur), occurs as a fine yellow, crystalline powder; insol. in water and alc., sol. in olive oil, freely sol. in carbon disulfide. Two pounds per 1000 cubic feet is used for fumigation. Sufficiently pure for medicinal use in dose of 4 Gm., 1 drachm, but *Washed Sulfur,* N.F. (Sulfur Lotum), is preferred. It is sublimed sulfur treated with ammonia water and thoroughly washed to remove the free acid. *Precipitated Sulfur,* U.S.P. (Milk of Sulfur), is prepared by precipitating sulfurated lime with acid. It is finer than sublimed sulfur and therefore more active, but is given in the same dose. *Sulfur Ointment,* U.S.P. (Ung. Sulfuris), contains 15 per cent of precipitated sulfur.

SODIUM THIOSULFATE

This salt is used as a reducing agent in photography, under the name of "hypo" or "hyposulfite." Taken by mouth, it acts as a *cathartic* (1 Gm. in water, every 2 hours if necessary; Petteys). It is used externally against *parasitic skin diseases.* For the prevention of the spread of *ringworm* of the feet, it has been advised to rinse these in 10 per cent sodium thiosulfate (W. L. Gould, 1931), or in 0.5 per cent sodium hypochlorite (Osborne and Hitchcock, 1931). Its *intravenous injection* is used against exfoliative and other *dermatitis,* especially those resulting from arsphenamine and other arsenicals and against manifestations of arsenical poisoning, and of poisoning by *metals* in general. Its success in dermatitis and arsenical hepatitis is about equal to that of nonspecific colloid therapy, and perhaps explainable by the separation of colloidal sulfur. Experimental investigations give no evidence that it has any value in arsenical or other metal poisoning (Muir *et al.,* 1940). It is a fairly good antidote to cyanide poisoning by forming thiocyanate; but this action is slow, so that it should be combined with more promptly acting agents, such as nitrite, which forms cyanhemoglobin.

Action in Arsenic Poisoning.—The use of thiosulfate against arsenical and other dermatitis appears to have been introduced by Ravaut, 1920. It was suggested that it converts the arsenic into less harmful compounds, such as the sulfide, but there is no chemical proof for this suggestion. Since thiosulfate has a similar beneficial effect on nonarsenical and nonmetallic dermatitis, it is quite conceivable that the action is not on the arsenic, but by the precipitation of colloidal sulfur.

Administration.—In arsenic and other metal poisonings the thiosulfate is injected intravenously as a 10 per cent solution in the dose of 0.3 Gm. of the crystallized salt on the first day, repeating the injection daily with increasing doses, namely, 0.45, 0.6, 0.9, 1.2 and 1.8 Gm. (McBride and Dennie, 1923). At the same time it may be administered by mouth, 2 Gm. twice a day, in 120 to 200 cc. of normal saline, which is said to diminish the tendency to vomiting.

Local Injection vs. Neoarsphenamine Irritation.—If neoarsphenamine solution accidentally enters the subcutaneous tissue, the injection of 5 or 10 per cent thiosulfate solution diminishes the irritation. This is probably due merely to dilution, and the injection of normal saline solution would probably be equally effective.

Thiosulfate against other metals has been tried, especially against mercury and lead poisoning (Dennie and McBride). Animal experiments indicate that it is ineffective (Haskell *et al.,* 1925; A. G. Young and Taylor, 1931), although it tends to form soluble double-salts with metals. *Sodium p-sulfhyril phenyl sulfonate* is also ineffective. *Sodium formaldehyde sulfoxylate* intravenously gives some protection against mercurial poisoning. By mouth it is effective only if administered within a few minutes (report, Council on Pharmacy and Chemistry, J.A.M.A., 1942, *120:*124).

H. M. Rabinowitz and Kahn, 1936, introduced intravenous injections of sodium thiosulfate against *obliterative thrombo-angiitis.* This was indorsed by F. W. Bancroft *et al.,* 1937, but its value appears questionable. R. V Theis and Freedland, 1940, proposed *sodium tetrathionate* for this purpose, but this would be dangerous, as it produces necrosis of the convoluted renal tubules in animals (Gilman, Philips *et al.,* 1947; report, Council on Pharmacy and Chemistry, 1947).

Fate.—Thiosulfate is distributed in the extracellular fluid. With intravenous injection, 70 to 80 per cent is recovered in the urine of dogs (A. Gilman *et al.,* 1946). The remainder is oxidized to sulfate.

Toxicity.—Lasch, 1919, states that sodium thiosulfate may be consumed without harm up to 12 Gm. per day. It would, however, produce catharsis, and possibly emesis. Intravenous injection of ordinary "C.P." sodium thiosulfate is often toxic, sometimes with fatal convulsions; but if the salt is purified by precipitating its aqueous solution with alcohol, it is tolerated in doses of 0.2 to 1.5 Gm. per Kg. (S. Goldblatt and Dennie, 1928).

Sodium Thiosulfate, U.S.P. (Sodii Thiosulfas; Sodium Hyposulfite), $Na_2S_2O_3 5H_2O$, is very sol. in water (1:0.5). Dose, 1 Gm., 15 grains, by mouth or intravenously.

SODIUM SULFITE

This is sometimes used as mouth wash against aphthae, and as 10 per cent lotion against ringworm and other parasitic skin diseases (pityriasis versicolor). The principal importance of the sulfite is its use in preserving foods. The quantities ordinarily employed are not directly harmful. Even much larger quantities do not act systemically, being rapidly oxidized to sulfates; but they may produce local gastric irritation by the liberation of sulfurous acid. Their harm is mainly indirect in that they improve the odor and appearance of spoiled meat so that it is sold as fresh. They are therefore properly prohibited.

Sodium bisulfite is most commonly used as antiseptic "*canning powder*." It requires an acid medium for the liberation of H_2SO_3, and is therefore not reliable. It destroys thiamine, but helps to preserve the ascorbic acid and carotene (Council on Foods and Nutrition, 1944, J.A.M.A. *125:355*).

Toxic Effects.—The harmlessness of ordinary quantities, even when continued for long periods, has been shown particularly by Rost and his co-workers (1904, 1912) and by Lehmann and Treutlein, 1909 (Long, 1912). The metabolism is not deranged. With larger doses by mouth, there are signs of gastro-intestinal irritation, due to the liberation of sulfurous acid (Jacobj and Walbaum, 1906). Toxic phenomena with histopathologic lesions occur when 0.1 per cent of sodium sulfite is added to the diet of rats; 0.25 per cent produces stunted growth, polyneuritis, atrophy of bone marrow, and other changes (O. G. Fitzhugh *et al.*, 1946). The absorbed sulfite is rapidly oxidized to sulfate (Rost and Sonntag, 1904), and it is only when this capacity is exceeded by large doses or intravenous injection that toxic effects appear. These lower the blood pressure, depressing the central nervous system, especially the medulla, the cardiac and arterial muscle without hemolysis or pathological lesions. The fatal intravenous dose for rabbits is 5.5 mg. per Kg. Death occurs by paralysis of respiration (Rost, 1914; Piva, 1933). In man, 1 Gm. produced no effects; 4 to 6 Gm. caused violent colic, diarrhea and circulatory disturbances (Rost; Franz, 1912).

Exsiccated Sodium Sulfite, U.S.P., Na_2SO_3, is sol. in water (1:4). Dose, 0.3 to 1.2 Gm., 5 to 20 grains. It oxidizes in air to sulfate.

SULFUR DIOXIDE (SULFUROUS ACID)

This was formerly used for disinfection of rooms, but is not reliable against bacteria (Koch), and is objectionable by bleaching colors. It kills most insects (McClintock, etc., 1911), including mosquitoes and bedbugs; and is therefore somewhat effective against certain insect-borne diseases, malaria, yellow fever, etc. It is quite ineffective against lice (Barot, 1918). Sulfur dioxide is generated by burning 3 pounds of sulfur for each 1000 cubic feet of space. To avoid danger of fire, the sulfur is placed in tin pans raised from the floor by bricks. Its action is materially greater when the air is saturated with moisture.

Toxic effects arise from leaking refrigerators, and from its use in disinfecting and bleaching. Large quantities occur also in coal smoke and become particularly objectionable in foggy weather. It is eventually oxidized in the air to sulfuric acid (T. W. Schaefer, 1907). SO_2 vapor produces strong irritation of the exposed mucosae, of the eyes, nose, and less so of the mouth. Its inhalation affects chiefly the upper respiratory tract, trachea and bronchi. The strong sensory stimulation often causes spasm of the glottis, which protects the deeper passages. Recovery from the effects of short exposure is rapid, but asthma may persist (Romanoff, 1939). Death may occur through edema of the lungs or of the glottis, but is uncommon, since lethal concentrations are so irritating that they are almost irrespirable (Henderson and Haggard, 1927).

Effective Concentrations in Air.—With man, inhalation of concentrations of 0.0006 to 0.0012 per cent by volume (1 per cent = approximately 28.2 mg. per liter) produces immediate irritation of the throat, and continued exposure often causes chronic catarrh (A. Fieldner and Katz, 1919). This may explain the apparent tolerance developed by continued exposure to low concentrations, since the increased secretions probably dull the respiratory reflexes (Henderson and Haggard, 1927). A concentration of 0.003 per cent may be tolerated for hours by men accustomed to the fumes, but sensitive people are immediately made ill, with irritation of the nose, sneezing, and cough (R. Kobert, 1906). The maximum concentration allowable for half an hour's exposure is 0.005 to 0.01 per cent (A. Fieldner and Katz, 1919). Inhalation of this concentration, daily for thirty days, by guinea pigs, mice and dogs results in loss of weight and an increase in the number of red blood corpuscles. Inhalation of concentrations of 0.04 to 0.05 per cent is dangerous, even for short periods. Concentrations of 0.05 to 0.06 per cent inhaled for one-half to one hour are fatal for cats (Lehmann, quoted by Rost in Heffter's Handbuch), and 0.06 to 0.08 per cent produces death in mice, guinea pigs and dogs in ten minutes to six hours (R. Kobert, 1906; A. Hamilton, 1925). With continued exposure of mice and guinea pigs to 0.0065 per cent (65 ppm), a third showed acute gastric distention by the ninth day. With 300 ppm most of the animals had distention and multiple hemorrhagic gastric ulcers by the third day, often with perforation (F. R. Weedon, 1942). Data for insects as well as vertebrates are given by Weedon *et al.*, 1939.

SULFONATED PETROLEUM DISTILLATES (ICHTHYOL AND SUBSTITUTES; AMMONIUM SULFOICHTHYOLATE)

Treatment of certain petroleum distillates with concentrated sulfuric acid and subsequent neutralization with ammonia results in tarry products, miscible with water or glycerin, and containing considerable quantities of sulfur compounds of alkyl radicals, *i.e.*, sulfonic acids (RSO_3H), sulfones (RSO_2R) and sulfur ethers or sulfides (RSR). The original product, "*ichthyol*," was introduced into dermatology by Unna, 1882, on the basis of a now disproved "reduction theory." Its use became a fad in dermatology, gynecology and proctology, but was not supported by critical control observations, and its popularity has waned. The limited usefulness of these products is due mainly to their physical, demulcent and emollient effects. They are reported to be somewhat astringent for mucous membranes or exposed tissues; and when concentrated, are mildly irritant, and stimulating and antiseptic. Their miscibility with water gives them some advantage for mucous membranes.

Epithelial hyperplasia is reported to follow repeated stroking the skin of mice or rabbits with a pencil dipped in ichthyol. The growth is somewhat atypical but not a hyperkeratosis (Mencarelli, 1930). Ichthyol was tried *internally*, especially against tuberculosis, on the basis of mistaken theories. Larger doses produce gastro-intestinal irritation and diarrha.

Origin.—"Ichthyol" was originally prepared from a Tyrolian bituminous shale containing the remains of fossil fish. Sulfonated oils have a long, although not prominent, history in medicine; for instance, "*Harlem oil*," *i. e.*, linseed oil saturated with sulfur. The *composition* varies considerably for the various products, and even for different samples of the same product. All, however, contain the three classes of sulfur compounds. The individual constituents have not been isolated. The total sulfur content of commercial "ichthyol" is about 10 per cent, of which about half consists of sulfides (sulfur ethers and mercaptans). The addition of acid to the ammonium salts precipitates a tarry mixture, "sulfoichthyolic acid."

Ichthammol (Bitumen Sulphonatum, Ammonium Ichthyosulfonate), similar to Ichthyol or identical with it, is a black viscid liquid, of strong characteristic odor. Sol. in water and glycerin, partly sol. in alc. and ether, miscible with fats.

THIOCRESOL AND THIOGLYCEROL

Reimann and Hammett believe that the sulfhydryl group (SH^-) is essential to cell production. Reimann, 1930, reported that *Thiocresol* application as a $\frac{1}{4}$ per cent ointment hastens the healing of ulcers and promotes the growth of skin grafts. *Thioglycerol*, CH_2OH $CHOH$ CH_2SH, acts similarly and appears preferable, as it is more stable. It is applied as a dressing of 1:5000 solution in glycerol, which checks excessive granulations; or as $\frac{1}{4}$ per cent ointment in hydrous wool fat. Wounds are reported to heal 20 per cent faster by its use. It should not be employed if malignancy is suspected or if the skin becomes irritated (review, L. E. Sutton, 1935). Watery solutions of *cysteine* were reported to have a similar effect (Brunsting and Simonsen, 1933).

Antagonism to Carcinogenic Agents.—Although sulfhydryl normally increases the rate of cell division, the injection of parathiocresol into mice delays or prevents the development of cancer by dibenzanthracene (Reimann and Hall, 1936).

Thiourea, $H_2N.CS.NH_2$, has been used in 1 per cent solutions for stimulating granulating tissue and for healing ulcers. The dressing should be discontinued when granulation is well established, to avoid excessive fibroblastic stimulation. Solutions may be boiled and keep well (W. R. Fearon, 1942). Its toxicity is low. The effects on the thyroid are discussed under that heading. Thiourea and other sulfhydryl compounds protect fats against oxidation and rancidity, but only in the presence of water. The reason for this is not clear (P. György *et al.*, 1943).

GLUTATHIONE

This tripeptide, glutaminyl-cysteinyl-aminoacetic acid, also contains a sulfhydryl group (SH^-) which changes readily to disulfide, and the reverse. It occurs in almost all animal tissues and in plants, and has been prepared synthetically. It probably plays an important role as acceptor for hydrogen, with the liberation of oxygen for oxidative processes, so that it catalyzes oxidations and reductions (Hopkins). Cells contain enzyme systems which work in both directions (review, Elvehjem *et al.*, 1942). It protects ascorbic acid against oxidation by ascorbic oxidase and by copper. Its role in living metabolism is not clear. Large doses continued through generations did not accelerate the growth of rats (Sherrod and Struck). It is not employed therapeutically.

Carcinogenesis and Growth.—The growth of cancer in mice is markedly slowed by diets deficient in cystine; the growth resumes on administration of cystine or glutathione. The growth of normal young mice or rats is affected in the same direction (C. Voegtlin *et al.*, 1936; Dyer and Du Vigneaud, 1936). Cystine is not essential to normal growth, however, as is *methionine* (Womack *et al.*, 1937).

Trichogenic Action.—A strain of hairless rats was not affected by feeding glutathione, but cystine produced temporary, and cysteine permanent, hair growth. The hairless condition was attributed to hereditary absence of an enzyme capable of breaking down glutathione (G. J. Martin and Gardner, 1935).

Blood coagulation is inhibited by the addition of glutathione. Cysteine and other thiol compounds are less potent (Kühman and Morgenstern, 1934).

Cystine, diamino-dithiolactic acid, forms 15 per cent of hair, 12 per cent of nails, in firm combination. Internally, it occurs in relatively small amounts as a constituent of glutathione. Its reduction yields cysteine, amino-thiolactic acid. Normal growth requires that the diet contain the cystine complex, although rats may form it from methionine (Tarver and Schmidt, 1939). Ingested cystine enters into cysteine, taurine, glutathione and keratin. Directly or through cysteine or glutathione, it liberates sulfur for the sulfonation and detoxication of injurious material (review, M. X. Sullivan, 1932). *Cysteine* and *thioglycolate* inhibit various antibiotic agents, penicillin, clavacin, penicillic acid, and some alpha, beta unsaturated ketones, menadione, etc. (Colwell and McCall, 1945).

Solutions of *Thioglycolic Acid*, $HSCH_2.COOH$, are used in "coldwave" hair treatments, up to 5 per cent in excess of ammonia. Some persons appear to have or develop allergic susceptibility, with rashes of the skin and mucosae. Severe cases may involve the blood count and liver function (L. H. Cotter, 1946).

CAUSTIC ACIDS

Dilute acids alter the solubility of colloids, and produce stimulation and irritation. Concentrated acids are corrosive, destroying tissues by direct chemical action. They convert the proteins into acid proteinates, which are soluble in concentrated and in very weak acids, but insoluble in moderately strong acids. Concentrated acids are therefore penetrating caustics, and moderately strong acids are astringent. *Connective tissue* is not dissolved, but is softened and rendered more soluble in boiling water. (This explains why meat becomes more tender on keeping.) Concentrated acids have a similar effect upon *epithelium.* Without actually dissolving it, they soften it in such a manner that it is readily detached. Dilute acids, on the other hand, harden it. Concentrated acids withdraw water from the cells. This affinity is so strong in the case of concentrated H_2SO_4 that it produces carbonization. All soluble acids and acid salts dissolve calcareous material, including the enamel of the teeth.

Members.—The most typical acids in regard to the local action are *sulfuric* and *hydrochloric acid. Nitric acid* produces the same effects, but differs from these in its chemic action, forming xanthoproteic acid from the proteins. *Sulfurous acid* also has a marked corrosive power. **Hydrofluoric acid** has a special toxic action. It causes intense pain, which may be delayed so that the patient does not know that he has been burned until a few hours later, when the area begins to smart (L. Schwartz, 1939). The pain then persists for several days. The destruction proceeds under the toughened coagulated skin, so that the ulcers extend deeply, heal slowly, and leave a scar (Schuermann, 1937). They may be treated by applying a paste of magnesium oxide and glycerin, and injecting a 3 per cent solution of calcium gluconate around the lesion. If the injection is made within three hours, it shortens by a third the healing time of experimental wounds from 40 per cent hydrofluoric acid, and lowers the incidence of suppuration by half. Daily injections are no more effective than a single treatment (A. Paley, 1941). Inhalation of air containing 0.02 per cent of hydrofluoric acid produces acute catarrhal irritation. Of the *organic acids,* those of the fatty series act similarly, but are weaker. *Trichloracetic acid* is the most corrosive of these. *Oxalic acid* has specific actions, probably by the precipitation of the calcium. The *compound acids*—such as ethyl-sulfuric, etc.—act like organic acids. The *aromatic acids* act partly as acids, but this is greatly obscured by their collapse action. The irritant action of the acids is shared to some extent by the *acid salts,* acid tartrates, acid sulfates, etc.

Uses.—The severe pain, deep penetration and extensive scar formation make acids undesirable cauterizants. *Nitric* and *trichloroacetic acids* form relatively firm eschars, so that their action is more circumscribed and less painful. *Sulfuric acid* has been made into a paste with inert powders (charcoal, sawdust, lead sulfate, etc.) to localize its action, but is still painful and difficult to control (Pusey, 1913). *Lactic acid* has a relatively mild action on normal tissues, but administration of insufficiently diluted lactic acid to infants produces esophageal corrosion, stricture and death (G. E. Young and Smith, 1944). *Chromic acid* may cause poisoning when used as a caustic. The destruction of proteins makes acids *antiseptic.* Even quite dilute solutions, such as the gastric juice, suffice to limit the growth of bacteria. Concentrated acids destroy them outright.

Local Effects of Dilute Acids.—These produce mild irritation and harden the epithelium without destroying it. They do not penetrate as deeply as the volatile organic irritants and do not cause nephritis.

They may be used in the form of baths, in the strength of about 30 cc. (1 ounce) of concentrated acid to the bath (30 gallons). They may be applied as lotions, especially formic acid in the strength of about 4 or 5 per cent in alcohol. Acids are used to harden the epidermis against excessive secretion of *sweat* (sweating feet); 5 or 10 cc. of concentrated hydrochloric acid are put in a basin of water and the feet placed in this until they become painful. This is done about twice a week. The irritant action of the volatile acids is sometimes employed to produce *reflex stimulation* of the central nervous system by inhaling vinegar, etc.

Poisoning by concentrated acids presents the usual phenomena of caustic poisoning. It is very painful. The "coffee-grounds" vomit is characteristic. Scar formation and stenosis are frequent. The prognosis and toxic dose depend upon the concentration and the parts affected. Sulfuric acid poisoning is the most common. The *treatment* consists in liberal dilution with water, and the administration of mild alkalis, preferably magnesia, but in its absence, of chalk or even sodium bicarbonate or soap. This should be followed by a demulcent, a tumbler of oil or, better, of thin flour paste.

Continued exposure to the vapors of acids, such as occurs in certain trades, gives rise to chronic bronchitis. They attack the teeth, especially the front teeth, which are most exposed; their destruction is often completed in two or three years. The necrosis may spread to the jaw, as with phosphorus. The local respiratory effects and systemic changes produced by inhalation of *toxic concentrations of hydrochloric acid* are described by Machle *et al.,* 1942.

PREPARATIONS.—*Hydrochloric Acid,* U.S.P., contains about 36.5 per cent of HCl; *Nitric Acid,* U.S.P., about 70 per cent of HNO_3; *Sulfuric Acid,* U.S.P., about 95 per cent of H_2SO_4.

Lactic Acid, U.S.P., is a syrupy liquid containing about 87.5 per cent of $CH_3.CHOH.COOH$. It absorbs water on exposure and is very soluble in water or alcohol. Used as a caustic, especially for dissolving diphtheric membranes. *Trichloroacetic Acid,* U.S.P., CCl_3COOH, occurs as deliquescent colorless crystals, very sol. in water and alc. A caustic, used especially against warts. *Osmic Acid,* OsO_4, is injected directly into the preferably exposed nerve in ½ to 1 cc. doses of 1 to 2 per cent solution to produce its degeneration for the relief of persistent neuralgias (Billroth and Neuber, 1885). The result is sometimes immediate, but more commonly it is not complete until after one or two weeks, or it may fail entirely. If it is successful, the effects persist for at least several months, when it may become necessary to repeat the injection. They are rarely if ever permanent. The local reaction is always painful but not serious. It is probably not advisable to use osmic acid in the presence of renal disease (Eastman, 1906).

THE LOCAL ACTIONS OF METALLIC SALTS

Metallic salts combine with proteins to form more or less difficultly soluble compounds containing varying amounts of the metal and proteins. The acid of the metallic salt is thus set free. Both factors are concerned in the actions. Some metal albuminates are almost insoluble in water; some are soluble in excess of protein, especially when neutral salts are present; others are not. If the precipitate is soluble, penetration and action are deep. If the precipitate is insoluble, as in the case of lead salts, penetration can not take place; the irritation is confined to the surface and an astringent action results. Lead is the most astringent metal ion; then comes aluminum; then iron; then zinc, copper, silver and tin, which are about equal; the most caustic is mercury. Hydrochloric acid is the most caustic of the liberated acids commonly used; then comes nitric acid; then sulfuric; then phosphoric; the weakest are the organic acids—acetic, citric and tartaric. By proper combination between the metals and the acids, one may obtain any grade of action from pure caustic to pure astringent.

The irritant, astringent and caustic actions are degrees of the same process. The astringent action always precedes the caustic action; and, consequently, by proper dilution one may obtain astringent effects from salts which are ordinarily purely caustic.

The caustic action of metallic salts was formerly used extensively, but has been largely abandoned. Most are not sufficiently powerful, others are too toxic (arsenic, antimony and mercury). Zinc chloride and antimony chloride (Butter and Antimony) are active caustics, but their scab is so soft that their action can not be kept within bounds. Silver nitrate in the form of sticks (Lunar Caustic), and to a less extent copper sulfate, are practically the only metallic salts used to produce a purely caustic action. *Arsenic,* were it not for its toxicity, would be a useful corrosive, for its action is so slow that it can be readily limited. *Silver nitrate* is easily controlled, since its action may be stopped at once by washing with NaCl, which converts it into AgCl.

Therapeutic Applications.—For use on *open wounds, ulcers, abscesses,* for the astringency and a mild stimulation leading to repair, silver nitrate is used extensively, also the soluble zinc salts and alum. They are applied in strengths of from ½ to 5 per cent. The insoluble astringents, zinc oxide and carbonate, bismuth subcarbonate or subnitrate, may be used as dusting powders, or in the form of ointments, 5 to 20 per cent. Absorption is fairly free from open surfaces, and calomel, bismuth, lead, etc., must be used with caution. Zinc oxide is safe. Astringents cause actual constriction of the mucous membranes, and may in this way bring about the complete disappearance of small *polypi.* The *mucous membranes* which are easily accessible to the local action of astringents are those of the mouth, conjunctiva, nose, genito-urinary tract and rectum. The same salts as for open wounds can be used, as also tannic acid. They are employed in somewhat weaker solution, as gargles, washes or injections. The usual strength is from ½ to 1 per cent, perhaps a fourth of this for the conjunctiva and urethra. double for vagina or rectum.

The usual concentrations for urethral injections are: Mild protein silver, 5 per cent; strong protein silver, 0.5 per cent; acriflavine, 1:3000; silver nitrate, 1:5000; potassium permanganate, 1:8000. They should not be long continued or they will keep up a urethral discharge (Pelouze, 1940).

Astringent treatment of the nasal schneiderian mucosa by tannic acid, alum, zinc salts or trinitrophenol hinders infection by viruses which ordinarily enter through this path (Olitzky and Cox, 1934). It was tried as prophylaxis against poliomyelitis and is quite successful in monkeys (C. Armstrong and Harrison, 1936), but proved disappointing clinically since the olfactory tract is rarely the portal of entry for the viruses in clinical cases (Sabin and Ward, 1941; American Orthopaedic Association, 1946).

Injury to Mucous Membranes.—The irritation provoked by astringents shows that they are not indifferent to cells, and may do harm; the injury is usually brief and easily repaired,

Fenton and Larsell, 1936, found for *frontal sinuses* infected with hemolytic streptococcus, in patients and experimentally in cats, that weak astringents (alum, tannic acid) generally decreased the severity of the infection, but that practically all antiseptics were harmful, as also histamine and acetylcholine. P. R. Cannon and Walsh, 1938, produced bronchopneumonia in rabbits by intranasal application of watery solutions of astringents; but these would not be so likely to reach the bronchi in man.

Ciliary Activity of the Upper Respiratory Tract.—On local application, in guinea pigs, 0.5 per cent silver nitrate is immediately fatal to the cilia; 2 per cent mercurochrome or 2 per cent zinc sulfate depresses severely; mild silver proteinate, 5 to 20 per cent, causes some slowing, partly by its viscosity. Of vasoconstricting agents, 0.1 per cent epinephrine causes some slowing (perhaps by its preservative), 3 per cent ephedrine has no effect. Of local anesthetics, 5 per cent cocaine hydrochloride had no effect, 10 and 20 per cent produced slowing but with good recovery. Of aromatic agents, 0.5 and 1 per cent menthol are mildly depressant, 0.5 per cent thymol and 1 per cent eucalyptol somewhat more so. Water also slows the beat (Lierle and Moore, 1934).

In the alimentary canal astringents are useful mainly by diminishing the results of inflammation; *i. e.*, the vomiting and diarrhea. Against *vomiting*, especially when caused by ulceration, bismuth subnitrate or subcarbonate seems to be the most useful. These act not only by their astringency, but also somewhat after the manner of inert dusting powders, affording an artificial protective covering to the walls of the viscus by adhering to them. Silver nitrate is also sometimes used in doses of about 10 mg. ($\frac{1}{6}$ grain), dissolved in water and given three times a day. Their action on *diarrhea* is entirely similar. Bismuth is again preferred; silver nitrate is often useful in the summer diarrhea of infants. Further details will be found under the respective metals.

Oligodynamic Action of Heavy Metals.—When applied directly or in pure solutions, especially to isolated cells, the heavy metals and their salts may produce marked effects in extreme dilutions. These are concentrated by adsorption on the cell surface. The action is sometimes beneficial, more commonly destructive.

The growth of *moulds* is markedly favored by traces of Zn and Mn (Raulin, 1870); the presence of zinc in a dilution of 1:25,000,000 increases the crop of the mould Aspergillus by more than 50 per cent (Bertrand and Javillier, 1912). On the other hand, the alga Spirogyra is killed by copper in a dilution calculated as 1:72,000,000 (Naegeli, 1893, who introduced the term oligodynamic action). Similar effects are produced by Hg, Pb, Sn, Fe and Ag, but Cu is by far the most toxic (Locke, 1895). The addition of metallic Hg, Ag or Pb to blood gradually produces hemolysis, while Cu hardens the corpuscles (Bechhold, Ascoli). If metals are placed in water, the containers, even after rinsing, impart to fresh water considerable catalytic and protein precipitant properties; the order of efficiency being: (most) Cu, Hg, Ag, Pb, Sn, Zn, Al, Fe, Mn, Pt (Falta and Richter-Quittner, 1921). Touching the His bundle of the mammalian heart with a rod of clean, polished copper produces instant heart block (v. Egmond, 1920). The oligodynamic action is due simply to the solution of traces of the metal (*f. i.*, silver, Freundlich and Söllner, 1928). It may be assumed that in these dilute solutions the metals exist first as colloidal metals, but that they pass rapidly into colloidal hydroxides and carbonates (Traube-Mengarini and Scala, 1912) with positive charge, which are therefore adsorbed (and detoxicated) by negatively charged solids (Bayliss). Charcoal and proteins give similar adsorption of the metals (A. J. Clark, 1937).

Astringent Styptics.—All metallic salts, the irritant as well as the astringent, and also the vegetable astringents, act as local styptics; *i. e.*, arrest capillary hemorrhage. They do so mainly by the formation of precipitates which occlude the lumen of the small vessels. They also injure the vessel walls and so tend to produce thrombosis. Astringents act only when they come into *actual contact* with the bleeding vessels. They can not act through a large clot of blood, and if such exists it must first be removed. They were formerly used internally with the idea of producing astringent action in remote places; iron was given by mouth to check bleeding in the uterus; but their action can not extend beyond the stomach, since they are precipitated or decomposed in the intestine. The *indications* for styptics are to lessen bleeding, especially capillary oozing. They have no effect on spurting arteries or large veins. They are sometimes injected into hemorrhoids, and have even been injected into aneurysms. Their injection into larger vessels may produce embolism.

Other Hemostatic Measures.—Any substance which gives a precipitate with proteins may act as astringent styptic; *e. g.*, dilute acids in concentrations which need not be caustic (vinegar and lemon juice). A number of purely mechanical measures favor the formation of clot; for instance, ordinary cotton or Pengawhar Djambe (this also contains tannic acid). Cobwebs were used in folk medicine, but are usually septic. The same effect may be obtained by fine powders which have a strong attraction for water. Cephalin and tissue extracts hasten coagulation *in vitro*, but are of little use on wounds. Other styptic measures are depression of the vasomotor center by narcotics; direct constriction of the vessels by the application of cold, or by drugs, such as epinephrine, *Microscopic observations* on the mechanisms of various hemostatic measures are discussed by Gramenitzky, 1937. *The efficiency of local styptics* has been tested experimentally by noting the quantity of blood lost when a skin wound is irrigated with the styptic (Hanzlik, 1918).

Methods of Testing Astringent Action.—Ordinarily, astringent action depends on the precipitation of the proteins (Mitscherlich, 1842; Lewin, 1881; Harnack, 1889). This may be tested directly; or by measuring the diminished extensibility of tissues, for instance the lungs (Dreser); or by the shortening of tissues which ensues when their proteins are precipitated (Crawford, 1918; tendon of rat tail, Komiyama, 1926); or by rendering red corpuscles resistant to hemolysis (Sollmann, 1920); or by the suppression of secretion on the frogs' skin (Schuetz); or by observation of blood vessels in the exposed mesentery (Heinz); or by the clinical response in catarrhs or diarrheas; or simply and with rather surprising accuracy, by the taste.

TANNINS AND VEGETABLE ASTRINGENTS

Tannins or tanic acids are a group of widely distributed vegetable principles, which give a blue or green ink color with iron salts, and which precipitate proteins, gelatin and connective tissue (as in the tanning of leather) and therefore act as astringents, styptics and antiseptics, the latter chiefly by depriving the bacteria of food. They are less destructive than the metals; being practically nontoxic, they are especially suited for use in the alimentary canal and for the treatment of extensive burns. They do not decrease peristalsis directly, but do so indirectly by allaying the underlying inflammation. Their employment in diarrhea dates back at least beyond the fourth century B.C. They form more or less insoluble compounds with many metals, alkaloids and glucosides, and are therefore used as antidotes. The different tannins are not equivalent in these respects. Some (which are perhaps misnamed), such as those of coffee and ipecac, are practically nonprecipitant. Others present differences in the firmness and solubility of the precipitate. The official tannic acid is obtained from nutgalls. In the course of its absorption, tannic acid is decomposed into the nonastringent gallic acid, pyrogallol, etc.

Varieties of Tannin.—Ordinary "tannic" or gallotannic acid is derived chemically by the elimination of a molecule of H_2O from two molecules of gallic acid (trihydroxy-benzoic acid, $C_6H_2.(OH)_3.COOH$). The numerous other varieties are of different composition, in many cases unknown. Some are compounds of gallic acid with sugar or phlorhizin.

As local astringent, tannic acid is used as 1 to 10 per cent solution, generally 5 per cent. Since watery solutions decompose readily, it may be prescribed as the *Glycerite* of *Tannic Acid,* U.S.P., which contains 20 per cent of tannic acid. This may be diluted extemporaneously. A 20 per cent ointment and suppositories of 10 per cent or less are used against hemorrhoids. The 5 per cent watery solution is used on bedsores (Latimer, 1934). *Bacterial cultures* are killed in twenty-four hours by 10 per cent of tannic acid; 5 per cent is ineffective (J. D. Martin and Fowler, 1934).

The tannic acid treatment of burns by repeated applications of freshly made 3 to 5 per cent tannic acid solution coagulates the devitalized tissue and forms a crust which protects its surface and prevents the pain and the irritation of drying and the loss of fluid by serous exudation, which is one of the factors of collapse. The effects are so striking that the treatment quickly obtained wide acceptance when it was introduced by E. C. Davidson, 1925. It became apparent, however, that it has limitations and drawbacks, and it lost favor rapidly—a common fate of methods of treating burns!

The treatment of burns by a 2 or 3 per cent ethereal solution of tannic acid is mentioned in Merck's Index of 1896, but it was little known. Davidson aimed to prevent the absorption of toxic protein decomposition products, but this does not play a significant part (Kapsinow, 1933). The *advantages* are that it is one of the most effective methods of relieving pain, preventing external loss of plasma and protecting against invasion of bacteria and secondary infection. It facilitates the handling of a large number of casualties and has saved many lives. Minor burns, however, do not heal more rapidly, and serious burns are reported to give a higher mortality with tannic treatment than with surgical cleanliness, pressure dressings and rest (D. B. Wells *et al.*, 1942). The *disadvantages* inhere chiefly in the character of the eschar, which develops slowly and requires frequent applications; it is inflexible, immobilizes or cracks; infection may spread unobserved under the opaque covering; the crust may produce pressure necrosis in circumferential burns; near body orifices, especially in the peritoneum, it dissolves and becomes infected; it delays the healing of third degree burns; the germinal epithelium may be injured, granulation tissue is not easily controlled, and unnecessary scarring may result (review, A. M. A. Councils, J.A.M.A. *125*:909). *Absorption of tannic acid* from large surfaces has been blamed for increased incidence of liver damage (see below). Painting the tannic crust with 10 per cent silver nitrate (A. G. Bettman, 1935) forms a drier, softer, thinner and more elastic eschar and so diminishes the difficulties, but does not remove them. Similar objections apply to coagulation crusts formed by 1 per cent gentian violet proposed by R. H. Aldrich, 1933, and by other dye mixtures. From industrial statistics it appears that the quickest healing of minor burns is secured by simply covering them with petrolatum-impregnated gauze and protecting with thick dressings, after cleansing with soap and water. Tannic acid and various medicated salves and emulsions averaged materially slower healing (McClure and Lam, 1943). In severe burns the dominant indication is to protect against excessive blood concentration through loss of fluid to the exterior and into the tissues. Intravenous injection of plasma is especially useful (Weiner *et al.*, 1936; H. N. Harkins, 1944). Pain should be controlled by adequate morphine.

Liver damage following clinical tannic acid treatment of burns, with focal necrosis of the cells, was described by W. C. Wilson *et al.*, 1938, and confirmed by others (Erb *et al.*, 1943). However, the same lesions occur clinically and experimentally with burns that had not been treated with tannic acid (Buis and Hartman, 1941) and in other forms of circulatory shock (Moon and Morgan, 1936). On the other hand, injection of tannic acid into animals that had not been burned produces similar and fatally severe focal hepatic necrosis (Wells, Humphrey and Coll, 1942; Baker and Handler, 1943); but this requires considerable amounts, so that it does not occur from oral administration (Handler and Baker, 1944) or even from application to denuded surfaces in rabbits (H. J. Robinson and Graessler, 1943). It is doubtful whether tannic treatment is dangerous on this account clinically unless the burn involves a third of the body surface (Saltonstall *et al.*, 1945). The risk is greatest if moist tannic acid dressings are kept in contact with burned surfaces for long periods (review, H. N. Harkins, 1945).

Constipative Action.—Administration of tannic acid has little effect on the movement of the normal intestinal tract, but tends to arrest diarrhea by allaying intestinal inflammation through its astringent action. This can be of only limited benefit if the cause of the irritation persists. The protein tannate precipitation occurs only within a restricted range of *p*H, ordinarily between 1 and 8.3, best between 3 and 5 (Sollmann, 1920).

The constipative action was studied on cats with the x-ray method by Hesse, 1913. In the absence of diarrhea, tannalbin has no effect on the intestinal movements beyond a slight delay in the emptying of the stomach; nor had it any influence on the diarrheas produced by milk feeding or senna; and but little on the catharsis of castor oil. However, it arrested certain dietetic diarrheas (bread), and that produced by the colon action of colocynth.

Astringent Plant Extracts.—Preparations of krameria, gambir (catechu), kino, etc., have been supposed to act more slowly than tannic acid because of the protective influence of their colloids. *In vitro,* they precipitate proteins just as readily; but the colloids probably protect the gastric mucosa somewhat by hindering its contact with the tannin. In practice, however, they have been generally displaced by the synthetic compounds.

Synthetic tannin compounds were devised with the aim of being insoluble in water and acid fluids, and soluble in alkaline solutions. This ideal was based on mistaken views as to the true reaction of the intestinal contents; but these properties have not been realized in any instance (Leech, 1920). All the commercial preparations are somewhat soluble in water; and most are about as soluble in dilute acid as in dilute alkali. Their tannin is dissolved, however, or becomes active quite slowly, whatever the reaction, so that they have little effect on the stomach and extend their astringency farther, into the intestines. The principal compounds, exsiccated tannin albuminate and acetyl-tannic acid, are about equally effective, and there seems to be little difference between them clinically.

Exsiccated tannin albuminates (*Albutannin; Tannalbin*), contrary to the prevailing opinions, dissolve rather better in artificial acid gastric juice than in bicarbonate-trypsin solutions. *Tannyl-acetyl esters* (*Acetannal; Tannigen*) are mixtures of varying quality; some specimens contain considerable free tannin. The best specimens appear fairly uniform and but slightly soluble and astringent in acid solution. Bicarbonate dissolves them and hydrolyzes them slowly (Sollmann, 1920).

Tannins of Beverages.—The small quantities of tannin ordinarily taken with the food and drink are not injurious; but large quantities (excessive tea drinking) are probably deleterious. The tannin of coffee is scarcely astringent, and therefore lacks this action.

Tannic acid interferes somewhat with *absorption,* chiefly by precipitating proteins. These combinations are again decomposed in the alkaline intestine, so that the interference is not large. The absorption of normal saline solution from a Vella fistula was accelerated by 0.01 per cent of tannin; 0.04 per cent had no effect; 0.1 to 1 per cent delayed absorption (Biberfeld, 1903). *Large doses* produce irritation and corrosion, especially if the stomach is empty, pain, vomiting, diarrhea or constipation.

The use of tannin as antidote is discussed under "General Toxicology."

The fate of tannic acid is imperfectly known; but it is completely decomposed, even on intravenous injection, into gallic and pyrogallic acid and other decomposition products before being excreted. These appear both in the urine and feces (E. Rost, 1897). Only the insoluble tannates pass in part undecomposed into the feces. With oral administration, the urine contains at most 1 per cent of the gallate of the tannin.

Preparations.—***Tannic Acid,** U.S.P. (Gallotannic Acid, Digallic Acid, Tannin), is an amorphous powder usually obtained from nutgall. Sol. (1:1) in water, glyc., or alc. Watery solutions gradually spoil (hydrolyze to gallic acid) on keeping. *Incompatible* with alkalis, alkaloids, salts of iron and most other metals, proteins and gelatin. Dose, as antidote, 1 Gm., 15 grains. Locally, for urethra, 1 to 2 per cent; vagina, 5 per cent; enema, 1 to 2 per cent; rectal irrigation (cholera), ¼ to ½ per cent; skin and ulcers, 5 to 20 per cent or the Glycerite. The U.S.P. *Glycerite* and *Ointment* contain 20 per cent tannic acid, preserved by sodium sulfite, and keep well.—*Gallic Acid* occurs in many plants, usually with tannic acid. Does not precipitate alkaloids. The reputed astringent effect is perhaps due to a small quantity of tannin which is usually present. Soluble in water, alc. or glyc. Dose, 1 Gm., 15 grains. Externally, 1 per cent, as weak astringent. *Acetyltannic Acid* (Acetannin, Diacetyltannic Acid, Diacetyltannin [H. Meyer, 1894]), Tannigen, Tannyl Acetate) is a yellowish- or grayish-white powder. Dose, 0.6 Gm., in capsules. *Albumin Tannate* (Albutannin, Tannalbin) is a yellowish-white powder containing about 50 per cent tannic acid (Gottlieb, 1896). Dose, 2 Gm., in powder or tablets, followed by water; infants, 0.3 to 0.5 Gm. in gruel.

Tannin-containing drugs include *Galla,* Nutgall; *Catechu, Gambir, Kino, Krameria* (Rhatany), and many others which are rather obsolete.

Diarrhea mixtures are "shotgun" prescriptions, generally containing an opiate, a tannin drug and an aromatic, sometimes with rhubarb and bismuth subnitrate.

NONVOLATILE ORGANIC IRRITANTS

Fixed organic substances produce local inflammation quite disproportionate to their apparent chemical reactions. They irritate the skin in various degrees, without astringent or caustic action, and are used in dermatologic practice and for counterirritation. They are also the cause of many accidental dermatites, especially industrially and by cosmetics. Pepper, capsicum and ginger are used as condiments, but the gastro-intestinal action of most of the others is too violent. Cantharidin causes marked irritation of the genito-urinary tract in the course of its excretion. Several insecticides may be discussed in this connection.

CANTHARIDIN

Cantharides (Spanish Flies) may be used for vesication and for prolonged counterirritation in pleurisy, neuralgic and rheumatic pains, etc. The irritation is active, but the penetration slow, so that the effects are gradual, with only moderate pain, and without involvement of the deeper layers of the skin. The blisters therefore heal readily and without scar. On mucous membranes and open wounds, the effects are more severe, leading to local necrosis, and slowly healing, suppurating ulcers. Internally, cantharis is highly toxic by gastro-enteritis and nephritis; even the absorption from a large blister may cause severe irritation of the kidneys and urinary passages. It is contraindicated in nephritis, and should never be used internally, although it was formerly employed as a diuretic, being one of the few drugs mentioned by Hippocrates. It injures the cells directly, not the capillaries, so that its nephritis is epithelial, not glomerular.

For vesication, it may be employed by spreading cantharides cerate on adhesive plaster, leaving a margin around the edges. It may require from six to ten hours to raise a blister, according to the thickness of the skin, its content in fat, and individual susceptibility. The plaster adheres poorly, and must usually be fixed with adhesive plaster. At the end of six hours (or two to four hours with children), the plaster is removed and the site dressed with petrolatum and sterile gauze. If the blister has already formed, the plaster should be carefully lifted without rupturing the vesicle, which is then pierced and dressed with an ointment, to prevent further pain, irritation or infection. By a "flying blister" is meant a series of small blisters raised along the course of a nerve by the application of successive plasters. When they are employed for counterirritation, they should not be applied directly over the inflamed part, but at some distance from it. They might otherwise render the inflammation more violent. Blistering has almost gone out of use. It is contraindicated in people of feeble condition, since it may then lead to ulceration.

Other Vesicants.—When cantharis is contraindicated—*e. g.*, in cases of inflammation of the urinary passages—it may be replaced by ammonia water or chloroform, which vesicate if their evaporation is prevented, as by covering with a thimble. These are rather more rapid in action, but much more painful than fly blister, and are therefore avoided if possible. Iodine, croton oil and mustard have also been used, but act too deeply.

Origin of Cantharidin.—Cantharidin is a crystalline anhydride of cantharidic acid. It forms soluble salts with alkalis, and these produce the same local and systemic actions. Cantharidin is contained in a number of insects, especially beetles. A similar substance exists also in some caterpillars. It is present in varying amount, even in the same species. It was isolated by Robiquet in 1810 from the Spanish "Fly" (a beetle—Cantharis or Lytta vesicatoria). It is contained in the soft parts, particularly the blood. More than two hundred species of vesicant beetles have been described in the United States (Swarts and Wanamaker, 1946). Cantharis was recommended by Hippocrates in dropsy and amenorrhea; it was popular in the days of heroic medication.

The hollow hairs of *caterpillars* produce local irritation; the active constituent is not known (F. Flury. 1929).

Absorption and Excretion.—Cantharidin is readily absorbed from all surfaces, even from the skin. It is excreted mainly by the kidneys (Eliaschoff); but since it irritates the gastro-intestinal tract when injected hypodermically, some must be excreted by this channel.

Symptoms of Poisoning.—When cantharis is taken by mouth, it produces successively: burning in the mouth, thirst, difficulty in swallowing, swelling and blistering of the tongue, asthma (Wade, 1929), salivation, nausea, vomiting, colic and sometimes bloody diarrhea and tenesmus (the gastro-intestinal symptoms may be less pronounced in rapid poisoning); kidney pain, burning in urethra, frequent micturition, albuminuria, casts, hematuria, painful erections, abortion, weak and slow pulse, chill, syncope and collapse. Recovery may occur in about five days, the urine returning to normal. Toxic effects have been produced by 0.6 Gm.; death by 1.5 to 3 Gm., but recovery has also occurred from much larger doses. Of cantharidin, 30 mg. is probably fatal.

The treatment of poisoning consists in gastric lavage, demulcents, opiates, alkalis and plenty of fluid, heat to the gastric and renal region, and warm baths. No oils or fats should be given by mouth; but the Arab physician Rhases advised washing the bladder with oil, through a catheter, and this would probably diminish the tenesmus.

Central Actions.—When injected into the circulation, cantharidin affects the *central nervous system,* producing short stimulation, excitement and increased reflexes, followed by paralytic symptoms, coma, etc. This central action is not often seen, being obscured by gastro-enteritis or nephritis.

Cantharidin Nephritis.—The kidneys are highly sensitive to cantharidin. Small doses act entirely on the glomeruli, which are greatly dilated; numerous leukocytes are found in Bowman's capsule. The urine becomes albuminous within half an hour after subcutaneous injection. The smaller doses increase its amount, while larger doses diminish it. The epithelium of the convoluted tubules is affected only by large doses, and rather late in the course of the poisoning. The interstitial tissue escapes entirely in the acute intoxication, and is but slightly changed even in the subacute form (Mürset, 1886; Pearce, 1913). The excretion of phthalein is delayed (Eisenbrey, 1913); the nonprotein nitrogen of the blood is increased (Folin, Karsner and Denis, 1912).

Hepatic changes and edema are seen in dogs, with fatal doses. Opie, 1912, found fibrinous clots in the lymph nodes of the hepatic region, around the injured cells, and considers their obstruction responsible for the edema. In their absence, the lymph flow is increased independent of the renal changes.

Polycythemia occurs after acute clinical or experimental poisoning. It sets in slowly and is rather persistent (Lipsitz and Cross, 1917; Morgulis and Muirhead, 1919).

Racial Tolerance.—The hedgehog, chicken and duck are remarkably tolerant to the nephritic action (Ellinger, 1900). This is not due to differences in the absorption or to destruction of the poison, for the cantharidin is found in the urine; nor are these animals immune to other nephritic poisons. The immunity to cantharides is only partial; even a single injection of a large dose causes chronic nephritis. But taking the fatal dose for man (30 mg. by stomach) as the unit, that for the same weight of hedgehog is about 3000. For the dog and cat it is about 2.5 (1 mg. per kilo); for the rabbit, about 45. This immunity to the nephritic action does not extend to the local action on the skin. In this respect, the hedgehog is even more susceptible than the rabbit, which is almost immune to the cutaneous action. The nephritic action is lessened by rendering the urine alkaline (Ellinger, 1905). In the rooster, cantharidin causes changes in the comb, analogous to those produced by ergot. Frogs are not susceptible.

Vesication in Animals.—Animals respond to irritation of the skin by cutaneous edema, rather than by vesication. This is probably due to anatomic differences. Of the experimental animals, the horse alone seems suited to test the action of vesicants (Ewe, 1920).

Tar cancer of rabbits is reported to have disappeared after three or four applications of cantharidin (R. Dubois and Ball, 1933).

Alopecia.—Cantharis is used in the treatment of baldness, in the form of tincture, greatly diluted with alcohol. It has little if any effect clinically. Hair growth is accelerated in rabbits by agents that cause local hyperemia (C. W. Hale, 1945). In undernourished rats, irritants activate the quiescent hair follicles; histamine is equally effective; thyroxin has similar results (E. O. Butcher, 1940).

Treatment of Impotence.—Many drugs have been employed for this purpose, but with questionable results. *Cantharis* produces erection through reflex irritation from the urethral mucous membrane. It is dangerous, since effective doses may set up nephritis. Many *essential oils* act in the same manner and are less dangerous and less active. Here belong, *e. g., daminana, ginseng, mint, garlic,* etc., and possibly *camphor. Strychnine* was thought to be effective by raising the tone of the spinal centers, but is probably useless, as are *phosphorus* and *arsenic. Alcohol, morphine, cannabis* and other narcotics may act as aphrodisiacs by stimulating the imagination. *Yohimbine* has a special action on the blood vessels.

Cantharides, N.F. (Cantharis; Spanish Flies, Russian Flies), is the dried insect Cantharis vesicatoria. Contains not less than 0.6 per cent cantharidin. The *Tincture*, N.F. (10 per cent), is added to liniments to prolong their local action; in hair lotions (1:50). It was used as a diuretic (0.1 cc., $1\frac{1}{2}$ minims), but is too dangerous. *Cantharides Cerate*, N.F., contains 35 per cent. *Cantharidin* is slightly sol. in water or alc., more sol. in chlorof., ether or oils. It may be employed as a blister, 0.05 to 1 mg. in a drop of oil, covered with simple plaster. The preparations of the British Pharmacopoeia are made with cantharidin.

Capsicum produces marked sensory irritation and rubefaction, but not usually vesication. It is used as a condiment and stimulant to the gastric mucosa, and externally as counterirritant against neuralgic pains, rheumatism and sore throat, as the ointment (25 per cent) or equal parts of tincture and soap liniment. The action is fairly lasting, and has the advantage that it does not injure the skin. Care must be taken that it does not get into the conjunctiva.

Capsicum (Red, Cayenne or African Pepper) is the dried fruit of Capsicum frutescens, grown in Africa. The dose of the *Tincture* (10 per cent) is 0.5 cc., diluted. The *Ointment*, N.F., contains 5 per cent of the oleoresin. The action of capsicum is due to 0.02 per cent of *Capsaicin*, a crystalline neutral principle. This produces persistent burning of the tongue in dilution of 1:100,000 (Nelson, 1901). The toxicity of capsicum is low: Gastric administration of 28 cc. of the oleresin to fasting young rabbits caused diarrhea and loss of weight, followed by complete recovery; 56 cc. were fatal (Carmichael, 1939).

Paprika, the fruit of C. annum, is a condiment (red pepper). It has little effect on gastric secretion, with normal stomach or in hyperacidity, but may cause marked increase in hypoacidity (von Berkesy, 1934).

Pepper (Piper) acts similarly to capsicum, but is less irritant. *Black Pepper* is the dried unripe fruit of Piper nigrum. *White pepper* is the ripe fruit, deprived of its outer pericarp. They contain the crystalline alkaloid piperine, a volatile oil, and a pungent resin. *Dose*, 0.5 Gm., 8 grains. *Piperine* (piperyl-piperidine) has been used as an antipyretic and carminative, 0.1 to 0.5 Gm., 2 to 8 grains, in capsules.

Anemonin is the irritant constituent of fresh plants of the buttercup family; for instance, the marsh-marigold, Caltha palustris (Kobert, 1917). It exists in Ranunculus scleratus mainly as a mother substance, proto-anemonin, which is volatile with steam. The structure of this and of anemonin have been determined and confirmed by synthesis (Asahina and Fujita, 1920).

Pulsatilla is the herb of Anemone Pulsatilla and A. liratensis; Europe. Its active ingredient is anemonin. The drug is very irritant, and is almost obsolete, but has been used against asthma, hemicrania, etc., in *doses* of 0.1 to 0.4 Gm. It has a depressant action on the excised uterus (Pilcher, 1916).

Mezereum is the dried bark of Daphne species. The active constituent is the anhydride of mezerinic acid. There is also a glucosid daphnin. The fluid extract is rarely used as an addition to liniments or plasters; also in Fldext. Sarsap. Co.

Arisaema (Indian Turnip; Jack-in-the-pulpit). The fresh corm of this plant is very irritating or "acrid" when chewed. This is probably due to the mechanical effect of its sharp calcium oxalate crystals (Lazenby, 1915; E. D. Brown and Anderson, 1918).

Euphorbium is the dried juice of Euphorbia resinifera; contains a gum resin. The active constituent is the resinous euphorbon, which resembles the active resin of croton oil (Boehm, 1915).

Croton oil (Oleum Tiglii) and *antimony and potassium tartrate* (see Index) were formerly used to cause pustule formation, as a more severe form of counterirritation; and to provoke reactions similar to those of nonspecific protein therapy. Pustulation is likely to lead to permanent scarring and is obsolete as a therapeutic measure.

POISON IVY

Contact with certain species of Rhus, common along roadsides, on fences, in woods and swamps, produces dermatitis (Captain John Smith, 1609), passing through hyperemia and itching to violent vesication, edema and suppuration, according to the specific sensibility of the individual. Many persons are practically immune, although a sufficient quantity of the isolated principle has never failed to produce the dermatitis. It is believed that the dermatitis is an anaphylactic phenomenon requiring sensitization by previous exposure. The susceptibility probably diminishes in time if it is not maintained by repeated exposure. It does not produce bronchial or other anaphylactic symptoms.

The active ingredient of all the species, *urushiol*, a mixture of closely related catechol derivatives, occurs as a resinous oil, contained in the sticky sap of the plants, which exudes when the plant is injured. It becomes inactivated by oxidation through *laccase*, a polyphenolase occuring in the sap of these plants (review, F. A. Stevens, 1945). It is so highly active that $\frac{1}{1000}$ mg. has caused severe vesication (Pfaff). It is not volatile, but it may be carried to some distance on the soot in the smoke of burning plants, and perhaps on dust (E. D. Brown), and by insects alighting on injured plants. None is present in the pollen (Warren, 1913; McNair). It may be conveyed by the hands or clothing from one person to another, as if it were contagious.

Toxic Species.—The most important are: Rhus vernix, synon. venenata (Poison Sumach, the most powerful); Rhus toxicodendron (Poison Oak); Rhus radicans and diversiloba (Poison Ivy); Rhus pumila (a Southern species)—all common in North America. These are largely subvarieties which may be changed into each other, and their toxic principle is identical (F. A. Stevens, 1945). It agrees with that of the Japanese lacquer tree (Rhus vernicifera). The common sumach, Rhus glabra, does not have this action. McNair, "Rhus dermatitis," Chicago University Press, 1923, gives extensive *references*.

Chemistry.—Pfaff, 1897, showed that the toxicity is not due to a volatile alkaloid or to a volatile acid, but that it is caused by a fixed oily substance, "*toxicodendrol*." McNair, 1923, obtained a purer extract, "*lobinol*," by differential solvents. Maijama *et al.*, 1922, isolated the pure substance "*urushiol*" from the oriental lac tree and identified it as a mixture of closely related o-dihydroxybenzene derivatives with unsaturated sidechains. Poison-ivy extracts yield apparently the identical substance (G. A. Hill *et al.*, 1934). It is soluble in alcohol and oils and is precipitated by lead acetate and other metallic salts. It is not destroyed by heating an hour at 100° C. (v. Adelung, 1912, 1913). On exposure to the air it becomes gradually oxidized, blackens, and loses its activity. This is due to the *laccase* of the sap. When it is separated from this enzyme by ether it is quite stable in slightly acid solution.

Symptoms.—The dermatitis begins after a latent period of one-half to nine, usually four or five, days, depending partly on the sensitiveness and thickness of the skin, partly on the quantity of the poison. The toxicodendrol may penetrate directly through the epidermis, for it may infect portions of the skin that are devoid of glands; but where these are present, the infection is usually more severe. The dermatitis does not spread beyond the area of contact. The cutaneous reaction begins with rubefaction, swelling and itching, and passes through the stages of macule, papule, vesicle and pustule, with leukocytic infiltration of the skin. There is also some systemic reaction: severe leukocytosis, febrile symptoms and slight renal irritation (McNair, 1916). The attack generally subsides in four to six days. Internally and hypodermically it produces gastric and intestinal irritation, proctitis, vulvitis and nephritis, but the systemic toxicity is relatively low.

Congenital differences of susceptibility are marked. Krause and Weidman, 1925, found half the subjects clinically immune to application of the plant to the intact skin; this was reduced to a fourth immune if the skin was scarified. They found no definite difference between blondes and brunettes, or obese and thin. Children are probably more susceptible than adults. At the age of fifteen years, 30 to 85 per cent give a positive skin test; of adults, 50 to 85 per cent. About half of those with positive test become affected on casual field exposure. All the chief races, including American Indians, appear about equally susceptible (review, F. A. Stevens, 1945). The tolerance varies from time to time, and is sometimes lost, and one attack generally leaves the skin more sensitive to future exposures. Infants at birth are not sensitive to rhus extracts (B. Shelmire, 1939), but they can be sensitized artificially (H. W. Strauus, 1931). Animals are relatively insusceptible (Krause and Weidman)- but guinea pigs can be sensitized to rhus (Simon *et al.*, 1934; Kile, 1936) and to urushiol (Landsteiner and Jacobs, 1936). 3 n-pentadecyl catechol may be used to test rhus hypersensitivity (H. Keil *et al.*).

Treatment of Ivy Poisoning.—Susceptible persons should avoid exposure to the plant, *e. g.*, by wearing rubber gloves. As soon as possible after contact, the area should be scrubbed thoroughly with soap and brush, followed by alcohol, to remove the unabsorbed poison. Nonirritating oxidizing agents have been recommended, such as 10 per cent sodium perborate in a special vanishing cream (L. Schwartz *et al.*, 1942), but its effectiveness is questioned (B. Shelmire, 1941). Frequent washing with a ferric chloride lotion (one part of the tincture to two of water) inactivates any toxicodendrol that is still on the surface, and tends to diminish irritation through the astringent effect. However, it sometimes causes extensive permanent pigmentation by the deposition of yellowish ferric granules in the epidermis and corium (Traub and Tennen, 1936). Calcium hypochloride, 1 per cent solution, may be used for decontamination of clothing and tools.

When the dermatitis has developed, its course is not materially influenced by treatment, but dressings wet with astringent lotions give some relief, especially if applied ice cold: aluminum acetate, 5 per cent; potassium permangante, 1:5000; tannic acid, 10 per cent (L. Schwartz and Warren, 1941). Saturated solution of lead acetate in alcohol was formerly popular, but implies some risk of lead poisoning. Salves should be avoided, especially in the early stages, since they might spread the area of infection by dissolving the toxicodendrol.

A large number of other measures have been tried, but without advantage (v. Adelung; McNair). They may be grouped as astringents (metallic salts, iodine, bromine, tannic extracts); analgetics (phenol, quinine); protective ointments and resins (grindelia); detergents (soap-paste dressing); alkalis (bicarbonate, borax, lime water); nondescript (expressed juice of "Touch-me-not" [Impatiens fulva]). Purified mushroom *tyrosinase* catalizes the oxidation of urushiol and related substances and diminishes their dermatitis. It is reported effective when applied to the skin (Sizer and Prokesch, 1945).

Desensitization for prophylaxis and treatment has been attempted by daily oral ingestion or intramuscular injection of gradually increasing doses of extracts of Rhus species, which may be used interchangeably. The results are controversial. Stevens, 1945, concludes that there is preponderant evidence that desensitization of limited duration but sufficient for prophylaxis can be produced by the oral method, but that this must be done slowly (in seven or eight months) or it involves danger of rashes and gastro-intestinal disturbances. Results with intramuscular injections are more doubtful. The extract must not come in contact with the epidermis. Overdosage causes fever and other constitutional reactions.

Clinical immunizations were attempted by Schamberg, 1919, and developed especially by Strickler, 1918 to 1923. *Chewing of the leaves* is dangerous. Three leaves produced severe stomatitis in two days; dermatitis on arms, hands and legs on the fourth day (R. K. Sassaman, 1945). A fatality has been recorded (Alumbaugh, quoted by McNair). Lighter cases develop pruritus ani, rectal irritation (S. H. Silvers, 1941) and aggravating hemorrhoids.

Other plants producing dermatitis include a number of tropical trees belonging to the same family—Lithrea caustica; Anacardium (active principle, cardol, an oily substance); Semecarpus, a variety of ornamental woods, especially tropical but also domestic, with marked difference of susceptibility (review, Senear, 1933). The sap of a variety of tropical plants of the Anacardiaceae, including the mango, produces allergic dermatitis, probably by an identical or related substance (E. D. Merrill, 1944). Mango susceptibility has been studied by H. Keil *et al.* "*Dhobie*" dermatitis in East India results from contact with linen marked by native launderers with a fluid from the fruit of Semecarpus Anacardium (N. R. Goldsmith, 1943). The latex of Semecarpus atra, the "acajou" tree of South Pacific islands, produces severe dermatitis; the natives believe that this may occur from sleeping under the tree (J. H. Hitch, 1944). *Manzanilla* tree dermatitis and keratoconjunctivitis are produced by the milky sap of a tree of the Euphorbiaceae, growing in the Carribean area (Snow and Harley, 1944). Some florists' and garden plants, primula, chrysanthemum, arbor vitae and many other plants (vanilla beans, Claveric, 1908); the fruit of the ornamental ginkgo tree (Starr, 1913), affect sensitive persons in the same manner. *Tomato-vine* juice has apparently produced mild dermatitis in susceptible individuals (Lain, 1918). *Primula dermatitis* is caused by direct contact with the common Chinese house plant, Pr. obconica, and a few other species. Nestler describes toxic crystals in the resinous secretion of the leaves. The treatment consists in cleansing with alcohol or ether, and the application of zinc ointment (O. H. Foerster, 1910; Rost, 1914). Primrose dermatitis has also been studied by Simpson, 1917.

CHRYSAROBIN

Chrysarobin is a mixture of neutral principles extracted from the "Goa powder," in cavities of a leguminous tree, Andira Araroba, of Brazil. It consists chiefly of chrysophanolanthranol, and yields *chrysophanic acid* on oxidation and is sometimes itself misnamed "medicinal chrysophanic acid." It is strongly irritant to the skin and mucous membranes, and is employed as 0.1 to 10 per cent ointment against chronic dermatoses, psoriasis, pruritus and ringworm, applied daily, but reducing the concentration as soon as an effect is obtained, else it may produce excessive and harmful irritation. A saturated ethereal solution is used on *warts*, painting it on daily and paring off the dead tissue. It should not be employed on the face, genitalia or scalp. The hands must be carefully washed. It stains the keratin of the hair and skin, and also linen, a brownish-violet color. This can be removed by chlorinated lime or benzol (Mankiewicz, 1916). Caution must be used lest it reach the eyes and produce violent conjunctivitis (or rather keratitis; Igersheimer, 1912) and corneal opacity. It is absorbed from the skin, and excreted partly as chrysophanic acid, which is easily formed by its oxidation, especially in alkaline solutions. The urine is therefore colored red by alkalis. A part is excreted unchanged, and causes renal irritation, casts and albuminuria. By mouth, 0.18 Gm. produces vomiting, diarrhea, renal pain and hematuria.

Chrysarobin has a strong affinity for oxygen, abstracsing it from the tissues. This was suggested as the basit of its action, the oxidation product, chrysophanic acid, being relatively inactive. The oxidation occurs only in water suspensions in the presence of alkali. Fats diminish its activity (Schamberg, Raiziss and Kolmer, 1915).

Chrysarobin, U.S.P., is an orange-yellow, microcrystalline powder, tasteless, odorless and irritating to the mucous membrane. Very slightly sol. in water, slightly sol. in alc. (1:385), partially sol. in fats. The *Ointment*, U.S.P., contains 6 per cent; that of the B.P. 4 per cent.

Anthralin, 1,8-dihydroxyanthranol, differs from chrysarobin by the lack of a methyl group. It appears to be an effective synthetic substitute for chrysarobin, possibly even more effective in psoriasis, somewhat less likely to cause local or systemic reactions, and producing less discoloration of the scalp or clothing.

It is applied as ointment in petrolatum, beginning with 0.1 per cent and increasing successively to 0.25, 0.5 and rarely 1 per cent, once or twice daily. Severe dermatitis may occur with 2 per cent. The same precautions should be used as with chrysarobin. It was introduced by Galewsky, 1916, and Unna, 1916, under the title *"Cignolin."* It occurs as a yellow crystalline powder, insoluble in water, readily soluble in organic solvents (H. Beerman *et al.*, 1933).

Resorcinol is related to this group (see Index).

PYRETHRUM FLOWERS ("INSECT POWDER")

Pyrethrum or Persian insect powder consists of the powdered flowers of Pyrethrum carneum and roseum, cultivated chiefly in Japan and the Kenya district of Africa. Dalmatian Insect Powder, which furnishes a relatively small supply, is derived from Chrysanthemum cinerariaefolium and appears to be closely related in composition and action. They lose activity on keeping. They should not be confused with Pyrethrum Root or Pellitory, the root of a related plant, Anacyclus pyrethrum, which is an obsolete sialogogue. The insecticidal action of insect powder is attributed to two esters, *pyrethrin* I and II, derived from a five-carbon ring, pyrethrolene (La Forge and Haller). Pyrethrin I is somewhat more potent than II. They are hydrolyzed by weak alkalis, including soaps. A third constituent, probably an oleoresin, produces dermal irritation; and an allergen, probably in the pollen, causes asthma and other allergic reactions in sensitive individuals, who are generally also sensitive to ragweed pollen (S. M. Feinberg, 1934).

Action on Invertebrates.—Insect powder kills all kinds of insects, but is used especially against bedbugs and roaches. An ointment, N.N.R., is employed against scabies (Sweitzer and Tedder, 1935). Extracts made with lipid solvents, dissolved (5 per cent) in oil or propylene glycol and liquified "Freon," are used in spray bombs with good results (Goodhue and McGovran, 1944). Emulsions are used on plants, and these are not injured by pyrethrum. Roaches react one and one-half minutes after application, first with great excitement, then with incoordination, progressive paralysis and death (Hockenyos, 1936). Caterpillars show similar symptoms. A considerable proportion of the insects recover within a day, so that they should be swept up and destroyed. Pyrethrins act on the neuromuscular system (Juillet *et al.*, 1924). The ventral nerve ganglia show vacuolization (F. Krüger, 1931). The heart of crayfish is sensitive to $1:10^{12}$ (Belleuvre, 1938). It is also effective against intestinal parasites of sheep and fowl (Perrot *et al.*, 1933).

The acute toxicity of the pyrethrins for mammals is relatively low, presumably because the esters are rapidly hydrolyzed to less toxic compounds, especially in the stomach (Chevalier and Ripert, 1927), so that there is little danger from the ingestion of small amounts (S. M. Feinberg, 1934). It may cause irritation of the skin about the anus. The toxicity is considerably higher with parenteral injections. These produce diarrhea, clonic convulsions, prostration and death by respiratory paralysis. Local application to the conjunctiva causes chemosis (Shimkin and Anderson, 1936; C. S. Leonard, 1942).

Rotenone, a crystalline neutral principle, is the active constituent of the root of *Derris elliptica*, a plant of Java. This and closely related 5-carbon ring derivatives occur in more than seventy leguminous plants, mostly tropical or subtropical (Acree *et al.*, 1944). They are used by the natives as fish poison, and in Sumatra as arrow poison. Rotenone and plants containing it are employed as insecticide for spraying vegetable crops, in amounts which do not leave sufficient residue to be poisonous to man, cattle or birds (Haag, 1931; J. A. Mathews and

Lightbody, 1936; Ambrose and Haag, 1937). Some insects are more susceptible than others. Toxic doses of rotenone administered to mammals cause vomiting, respiratory depression, incoordination, clonic convulsions, muscular tremors and death by depression of respiration. The fatal dose by mouth is fifty times that of peritoneal injection (Shimkin and Anderson, 1936). The oral toxicity of derris to mammals appears greater than corresponds to its rotenone (Ambrose and Haag, 1936), but 0.2 Gm. per Kg. is not fatal (H. H. Shepard, 1939). Inhalation of the dust may produce fatal pulmonary irritation. Feeding of small doses produces fatty changes in the liver. It is not anthelmintic (Haag, 1931). The toxicity of rotenone and its derivatives for *gold fish* has been studied by Gersdorff, 1930.

MISCELLANEOUS INSECTICIDES

Many substances are toxic to insects, but their practical efficiency varies with conditions, depending on their physical properties, volatility, spreading power, etc., as well as chemical toxicity (W. Moore and Graham, 1918; Shepard, 1939; historical, R. C. Roark, 1935), and these must be weighed against the possible dangers to man and stock.

Commercial insecticide sprays contain principally pyrethrum dissolved in petroleum distillate, supplemented by cheaper poisons, such as paradichlorobenzene ("PDB"), thiocyanates, derris extract, isobutyl undecylenamide, flavored with citronella or pine oil. All these can irritate the skin and produce toxic and even fatal effects if enough is inhaled (L. Schwartz and Warren, 1939).

For field crops and orchards, the most useful agents are lead and copper arsenates, with calcium polysulfide for scale insects; *for horticulture*, nicotine, hellebore and sulfur; against *roaches and ants*, sodium fluoride, borax, cresols and insect powder; against *moths*, naphthalene and camphor; for *house flies*, sodium fluoride and arsenic trioxide; the toxicity of organic compounds is generally proportional to their volatility (W. Moore, 1917). Paradichlorobenzene is used against fly larvae. *To repel mosquitoes*, odorous volatile oils are more or less efficient, presumably by obscuring the human odor (Bacot and Talbot, 1919). Esters are generally more potent than the corresponding alcohols, and these surpass their hydrocarbons (W. Moore, 1934). Mixtures of dimethylphthalate derivatives are more effective (see below). *Bedbugs* are killed by painting all crevices with alcoholic solution of mercuric chloride and dusting with insect powder. Against *lice*, "DDT" is the agent of choice (see below). Mercury, staphisagria, phenol, etc., are effective against limited infections, but they are too toxic and irritant for extensive application. Naphthalene and volatile oils stupefy and paralyze the parasites, but they are likely to recover subsequently. Acids are definitely fatal. Sulfur dioxide is effective (Knaffl-Lenz, 1915). Oiling of underwear destroys the lice mechanically (1 cc. of oil per 4 square inches of medium weight underwear). Creosote and especially heliotropin (piperonal) may be applied in theobroma oil (W. Moore, 1918).

Dimethylphthalate is a potent insect repellant, useful against mosquitoes, mites and leeches (J.A.M.A., 1945, *128:* 30). Clothing may be impregnated with a 5 per cent emulsion, or the repellant may be applied as a spray or thin film, which remains effective for three or four washings. Solutions when *swallowed* produce irritation of the buccal mucosa, nausea, vertigo, vomiting, early coma and fall of blood pressure (Doehring and Albritton, 1944). Dimethyl and dibutyl phthalates are used to repel parasitic *mites*, as is also benzyl benzoate. The latter is lethal to the cercariae of schistosoma (E. C. Faust, 1946). *Other effective insect repellants* are n-butyl mesityl oxide oxalate and 2-ethyl-1, 3-hexanediol (review, F. S. Phillips, 1946)

CHLORINATED DIPHENYL ETHER ("DDT")

This substance, dichloro-diphenyl-trichloroethane, is highly toxic to many insects and is expected to revolutionize insect control. It is most effective as "louse powder," and is also satisfactory against mosquitoes, larval and adult, chigger mites and many others. It is applied as a 5 per cent dust or emulsion, and remains potent on the surfaces for at least three weeks, even after several launderings, acting as prophylactic as well as eradicator. It belongs to the group of chlorinated hydrocarbons and resembles them in its effect on mammalian heart. It is harmless to man when properly applied, but high doses are toxic when absorbed from oily solutions by the skin. Powders and aerosols are not absorbed, and no ill effects ensue from the small amounts that are inhaled. Few unquestioned cases of poisoning have been reported, in spite of its extensive employment, but this may be credited to observance of proper precautions. The "joint statement" of the U. S. Army and U.S.P.H.S., 1945, J.A.M.A., *128:*36, points out that indiscriminate spraying would kill useful as well as harmful insects.

The substance was synthesized by Othmar Zeitler, 1874. It was introduced as insecticide, with the trade name *Gesarol*, by Geigy of Basel. It is a fine powder of faint floral odor, insoluble in water, soluble in many organic solvents. It is chemically rather inert, very stable, and does not volatize materially. It adheres to surfaces, so that it is not likely to become detached as dust.

Action on Insects.—The susceptibility of different species varies considerably; it is greatest for those with chitinous cuticle, which probably adsorbs the poison. Larvae of mosquitoes are highly susceptible, those of flies but little, adult flies considerably. It enters through the tarsi, and kills by excitation and paralysis of the central nervous system. When insects make contact "they begin to fly around in erratic circles for ten to twenty minutes, then fall to the ground, apparently paralyzed, and die several hours later." In roaches the action appears to be on the region between the ventral nerve cord and the nerve endings, while nicotine acts on the ganglia (Yeager and Munson, 1945; review, F. S. Phillips, 1946). The roaches show continuous twitching. This persists in amputated legs and is therefore peripheral. Tremors occur with much lower concentrations. These are associated with high frequency trains of axon spikes in the afferent nerves and are attributable to afferent bombardment of the motor neurons (Roeder and Weiant, 1946). It has similar actions on *crustaceans*, producing repetitive discharge of motor fibrils to a single impulse, resulting in tetanus. Pyrethrin and veratrine produce analogous effects. They are suppressed by calcium ions (J. H. Welsh and Gordon, 1946). Daphnia is immobilized by $1:10^9$ to 10^7 (B. G. Anderson, 1945).

Application as Insecticide.—Dusting with 1 to 5 per cent powder is most effective against *lice* and *chigger mites. Mosquitoes* are controlled by applying it to the walls as 5 per cent emulsion by brushing or, more conveniently, as "aerosol" sprays of liquefied Freon. Ants, roaches, bedbugs, flies, fleas and ticks may be treated with 5 per cent powder or solution in kerosene, with particular attention to cracks. A D.D.T. paint is effective against "fouling" of ships by barnacles.

Clinical Toxicity.—In spite of the inherent toxicity of D.D.T., its use as aerosol spray in 1 to 3 per cent solution in 10 per cent cyclohexanone with 89 to 85 per cent of Freon is not injurious; nor is dusting with 10 per cent dilutions in inert powders. Experimental exposures show that there is a considerable margin of safety. Contamination of food must be avoided (P. A. Neal, von Oettingen *et al.*, 1944, 1946). Oily solutions are absorbed through the skin. Occasional contact is not harmful, but large doses produce serious toxic symptoms in animals. The powders are not irritating to the skin, solutions only mildly so (Draize *et al.*, 1944). There is more danger from the use of unsuitable solvents, especially chlorinated hydrocarbons.

Clinical symptoms in mild cases include nausea, vomiting, anxiety, stiffness and pain in the jaws, sore throat for several days (M. I. Smith, 1946). A group of persons poisoned by mistake for baking powder developed giddiness and weakness in one to two and a half hours. All recovered in forty-eight hours (Mackerras and West, 1946). Fatal poisoning in a child, reported by K. R. Hill and Robinson, 1945, indicates that 150 mg. per Kg. is fatal. This is similar to the LD_{50} dose in animals (M. I. Smith and Stohlman, 1945).

Toxic Effects in Animals.—D.D.T. is acutely toxic to mammals on oral administration of 150 to 750 mg. per Kg. of body weight. It produces anorexia, tremors, of long duration, convulsions, depressions, paralyses and death (G. Woodard *et al.*, 1944). The mammalian symptoms correspond to ablation of the cerebellum and cortex, and the cerebellum shows pathologic changes in chronic poisoning (Crescitelli and Gilman; review, F. S. Phillips, 1946). The myocardium is sensitized to fibrillation, as with other chlorinated hydrocarbons (F. S. Phillips *et al.*, 1946). In dogs, daily doses of 100 mg. per Kg. result in fibrillary contractions of skeletal muscles, passing into tetany, suppressed by calcium gluconate injection (Z. Vaz *et al.*, 1945). Larger doses (150 to 250 mg.) produce severe neurologic symptoms attributable to cerebellar dysfunction (B. P. McNamara *et al.*, 1946). Animals that survive several weeks have moderate central necrosis in the liver, possibly with reparative hypertrophy. The central nervous system does not show significant lesions (A. A. Nelson *et al.*, 1944); but Pluvinage and Heath, 1946, describe diffuse damage to the ganglion cells in acute poisoning of cats. Mice are more susceptible than rats; guinea pigs, dogs and monkeys are much more resistant (P. A. Neal *et al.*, 1945). Goldfish and frogs are considerably more susceptible than mammals (M. M. Ellis *et al.*, 1944). It has no effect on tissue cultures of chick embryos and of the brain and spleen of rats, even when the crystals are in actual contact with the cells (W. H. Lewis and Richards, 1945).

The toxicity for mammals and insects does not differ widely on the basis of tissue concentration; the relatively low toxicity for mammals is due chiefly to slow absorption (J. M. Tobias *et al.*, 1946).

The fate, distribution and excretion of D.D.T., as well as the acute and chronic toxicity for animals, were studied by M. I. Smith and Stohlman, 1944; E. P. Lang and Fitzhugh, 1946; and by Ludewig and Chanutin, 1946. Significant amounts are stored in the body fat, especially if fed in oily solution to dogs (G. Woodard *et al.*, 1945). The milk of poisoned animals contains enough to produce typical toxic symptoms in the sucklings (Telford and Guthrie, 1945). Rabbits fed with D.D.T. excrete di (parachlorophenyl) acetic acid in the urine (W. C. White and Sweeney, 1945).

Tetradichloro diphenyl ethane, "T.D.E.," "*rhothane,*" a related compound, has a similar toxicity for anopheles larvae (Deonser and Jones, 1946). Other related compounds have been studied by M. I. Smith, Bauer *et al.*, 1946.

Betabutoxy-beta-thiacyano-diethyl ether (*Lethane* 384) is safe and highly effective against all household insects, including roaches and moths (E. C. Faust, 1946).

Hexachlorocyclohexane, $C_6H_6Cl_6$, "666," "*benzene hexachloride,*" equals or surpasses D.D.T. against most insects, but has a disagreeable odor. The four isomers which compose the technical product differ widely in potency. The gamma form ("gammexane") is many hundred times stronger than the others on insects, and there are also great differences in mammals; the gamma is convulsant, the delta depressant (review, F. S. Phillips, 1946).

IRRITANT VOLATILE OILS

The volatile (or "essential") oils which give their distinctive odor to plants are usually mixtures of hydrocarbons of various groups, generally containing terpenes and oxidized aromatic derivatives. The balsams and resins which contain volatile oils may be included in the group. These oils occur in numerous plants and determine their use as flavors, aromatics, carminatives, antiseptics and irritants. Their chief application is for their local effects, consisting of deep irritation with a minimum of tissue destruction. The sensory stimulation is followed by some anesthesia. They exert a favorable influence on chronic inflammations, partly by their mild antiseptic and irritant action and partly by chemotactic attraction of leukocytes. In acute inflammations they are more likely to do harm. Their antiseptic action is relatively weak, since they are but slightly soluble in water. After their absorption they are excreted mainly in combination with glycuronic acid (Matzel, 1905). They irritate the kidneys, produce diuresis and act as urinary antiseptics.

Composition.—The terpenes are aromatic, cyclic compounds of the general empirical formula, $C_{10}H_{16}$. Related to them are the semiterpenes (C_5H_8); sesquiterpenes ($C_{15}H_{24}$); and diterpenes ($C_{20}H_{32}$). Other constituents are oxidation products of these and aromatic phenols, ketones, aldehydes, acids and their compounds.

The antiseptic effects have been investigated especially by Kobert, 1906; Rippetoe and Wise, 1912.

Antiseptic Action of Aromatic Fumes.—The smoke of burning wood has been used since antiquity for "purifying" or "curing" meat; the smoke of aromatic resins, incense, etc., for "purifying contaminated air." Macht and Kunkel, 1920, confirmed that these fumes are feebly antiseptic. It is improbable, however, that concentrations which could be inhaled without injury to the mucosa would be directly injurious to bacteria.

The fungicidal action is not necessarily proportional to the antibacterial action (H. B. Myers and Thienes, 1925). *Thymol* is especially effective against yeasts, and was tried clinically against fungal infections of the skin and mouth, but apparently with only limited success. H. B. Myers, 1937, claimed fair clinical result in actinomycosis from local application of 10 to 20 per cent solution of thymol in olive oil, together with oral administration of 2 Gm. daily.

Volatile oils (particularly those enumerated as urinary antiseptics) are used in various *subacute and chronic inflammations* and are said to lessen aseptic inflammations at points remote from the site of their application, by decreasing the formation of exudates and by hastening their absorption. The explanation may be *chemotactic attraction* for leukocytes (Hamburger, 1912).

Systemic Actions of Volatile Oils.—The principal central effects of volatile oils are reflex. With the ordinary doses, no direct action whatever can be observed. Large doses act on the nervous centers, especially the brain and medulla. These are first stimulated, then depressed. The details have been investigated, especially by Hildebrandt, 1901 and 1902, and Geinitz, 1912. The degree of *stimulation* varies for the different oils. Turpentine has scarcely any effect, while absinthe, thujon, fenchon, carvon and camphor produce violent epileptic convulsions (see Index for Absinthe and Camphor). The *depression* is more uniform: the majority (valerian, fennel, chamomile, eucalyptus, mint, rosemary, sabinol, citral, turpentine) diminish the reflex excitability, so that large doses entirely prevent strychnine convulsions in rabbits. The effective doses are, however, too large to make it possible to employ this action in man.

Curare actions have been studied by Hildebrandt and by Matzel; *cardiac effects* by H. Schwalb, 1912. *Isolated intestinal segments* are stimulated by oil of anise, turpentine and chenopodium, in concentrations of 1:50,000 to 1:25,000. Higher concentrations of all volatile oils depress the movements (Muirhead and Gerald, 1916). If volatile oils are injected *hypodermically*, they produce the reflex action in a more marked degree than when they are applied to the surface of the skin. Later their systemic, and still later the renal, actions take place. *The hemolytic action of terpenes* varies with the surface tension; but the alcohol or ketone character also has an influence (Ishizaka, 1914). Some form *methemoglobin*, especially the terpenes, ketones and aldehydes with unsaturated sidechains or methylene groups (Dessemontet, 1927).

OLFACTORY STIMULANTS

Odorous substances produce reflex effects. Pungent and aromatic drugs cause prompt medullary stimulation, increasing the respiration and blood pressure, and slowing the pulse. They are used in fainting, as *Tinctura Lavandulae Composita* (U.S.P., B.P.) and Aromatic Ammonia, the latter often by inhalation. Any pungent substance may answer; the burning of a feather under the nose of the patient is a popular household measure.

The respiratory reflex for ether, carbon disulfide and ammonia appears to be transmitted chiefly by the olfactory nerve, the trigeminal path being only supplementary (Ciurlo, 1933). Substances which produce sneezing (*sternutatoria* or *errhines*) cause reflex stimulation, presumably trigeminal. Their use as counterritants in nasal catarrh is obsolete, as they are more likely to do harm than good.

HYSTERIC SEDATIVES OR ANTISPASMODICS

Asafetida, valerian, musk and similar drugs of marked and peculiar odor have been used since antiquity as sedatives in hysterical and similar nervous conditions. They are often effective, presumably by olfactory and psychic reflexes. Modern psychiatric methods, aiming at the causes, give better and more permanent results. Sydenham (1624–1689) attributed their effects to their "strong and noisome smell, to recal the exorbitant and deserting Spirits to their proper Stations." Asafetida is also carminative, and has been used by mouth and enema (emulsion) in tympanites; but it imparts its odor to the excreta and eructations. Large doses (½ ounce) have been taken without other noticeable effects. Large doses of valerian produce systemic action, but it is doubtful whether these occur with the ordinary doses. Valerian was formerly used as a perfume and as a spice for meat, and asafetida was reported to be employed as condiment in Persia.

Preparations.—*Asafetida* is the gum-resin obtained by incising the rhizome and roots of species of Ferula. A soft, yellowish-brown mass of characteristic odor, bitter and acrid taste. Dose, 0.4 Gm., best as pills. When rubbed with water, forms the milk-white *Emulsion of Asafetida*, 4 per cent, used especially as enema against tympanites in dose of 15 to 60 cc. (½ to 2 ounces).

Valerian (Valeriana) is the dried rhizome and roots of Valeriana officinalis. Dose of the (20 per cent) *Tincture of Valerian* is 2 to 4 cc. (½ to 1 drachm). Valerian contains ½ to 2 per cent volatile oil, valeric and other organic acids; tannin and resins. The oil consists of esters of valeric (valerianic) acid, especially with borneol. These are probably the bearer of the action, but this was doubted by Haffner, 1929. Free valeric acid and its salt are quite ineffective. The fresh root is also ineffective, the esters being formed only during drying by the action of oxidases (Kochmann, 1904). The juice of the fresh plant produces different effects from the dried valerian (Pouchet and Chevalier, 1905). The esters again deteriorate by oxidation on keeping. Certain synthetic esters are said to be more stable. *Injection of valerian oil* produces the usual effects of volatile oils (Pouchet and Chevalier; Kionka, 1904); in small doses, psychic exaltation and rise of blood pressure from cardiac and vasomotor stimulation; in larger doses, central sensory and motor depression. Petlach, 1938, observed no apparent effect of valerian or borneol on the central nervous system of guinea pigs. Large doses cause death by hepatitis. *Excised frog heart* is weakened by very dilute solutions, and arrested by stronger solution of valerian or borneol (Petlach, 1938). *Excised uterus* is stimulated by valerian oil (Pilcher, 1916). *Excised intestines* are depressed by valerian oil (Delzell, Burman and Pilcher, 1916). *Synthetic Valerian Esters.*—Amyl valerate; Bornyval (borneol isovalerate); and Valyl (valeryldiethylamide) have been introduced.

Valerates (*Valerianates*) have little value. They are given in *doses* of 0.06 to 1 Gm., generally in capsules. They are colorless crystals of a valerianic odor, readily soluble in water; Zinci Valeras, Ammonii Valeras.

Minor drugs of this group include Sumbul (Musk Root), Moschus (Musk), Castoreum, Cataria (Catnip), and Symplocarpus (Skunk Cabbage). The actions of *musk* have been studied by Y. Takayama, 1930. They are so slight that they would not produce any therapeutic effects.

MUSTARD OIL GROUP

The sharp taste and irritant action which *black mustard seed* develops on contact with water are due to the formation of the *volatile mustard oil, allyl isothiocyanate,* C_3H_5NCS, by the action of the enzyme *myrosin* on the glucoside *sinigrin* (potassium myronate), which by itself is not irritant. The ferment action is favored by warmth, but arrested by boiling water. *White mustard* contains a similar ferment and glucoside, *sinalbin,* which yields an analogous volatile oil, acrinyl isothiocyanate, in much smaller quantity. Mustard seed also contains about 25 per cent of bland fixed oil. Similar sulfur-containing volatile oils are formed in other cruciferous plants, such as radish, horseradish, cress, shepherd's purse; and in onion and garlic. Dichlordiethyl sulfide, "*mustard gas*" (see Index) is a much more violent irritant belonging to the same group.

Externally, mustard oil produces more prompt, more violent and more penetrating irritation than the other volatile oils. Mustard preparations are used for counterirritation, in neuralgia, rheumatism and pleurisy, generally as "mustard plaster," mustard poultice or alcoholic solution of mustard oil. They cause rubefaction if the application is stopped as soon as marked tingling is felt. Longer contact may result in vesication and slow-healing ulcers. Since the oil is absorbed into the skin, its action progresses somewhat after the mustard is withdrawn.

Black Mustard, U.S.P. (Sinapis Nigra), consists of the dried ripe seeds of Brassica nigra, B. juncea, or varieties of these species, yielding not less than 0.6 per cent of allyl isothiocyanate. Dose, emetic, 10 Gm., 2½ drachms. **Mustard Plaster,* U.S.P. (Emplastrum Sinapis, Charta Sinapis, Mustard Paper), is a mixture of defatted black mustard and an adhesive, spread on paper or cotton cloth. When it is moistened thoroughly with warm (not hot) water, and applied to the skin, it produces redness and a decided sensation of warmth within a few minutes. It may be left on for fifteen to thirty minutes; or five to ten minutes if the skin is sensitive. Powdered mustard is applied as a *poultice,* mixed with 1 to 10 parts of flour and enough tepid water to make a paste; it may also be sprinkled on the surface of the ordinary linseed poultice. It is used in *foot baths* for preventing colds (1 to 2 ounces to a gallon); and in general baths for infantile coma (large tablespoonful to small bath). *Allyl Isothiocyanate,* U.S.P., C_3H_5NCS, is the *volatile oil of mustard,* distilled from macerated mustard seeds or prepared synthetically. It is a pale yellow liquid, having a pungent odor and taste. It should not be smelled or tasted unless it is highly diluted. It may be used as a counterirritant in $\frac{1}{10}$ to 2 per cent solution in 50 per cent alcohol (Herzfeld, 1909). Mustard oil is more irritant in aqueous than in oily vehicles (Sollmann). A 2 per cent suspension in 3 per cent tragacanth paste represents an effective counterirritant, equal to a 3 per cent ointment (Ewe, 1920).

Mucous Membranes.—Mustard oil in vapor as well as in substance or solution causes strong irritation of the conjunctival, nasal and bronchial mucosae.

A 15 per cent solution of mustard oil in liquid petrolatum produces marked *chemosis* if a single drop is applied to the conjunctiva of a rabbit. The edema begins in a few minutes and becomes maximal in half an hour, and then fades slowly, with complete recovery in one to two weeks, so that the experiment may be repeated a number of times, with fairly similar results. This has been used to study modification of inflammatory phenomena by analgetics and anesthetics (Chiari and Januschke, 1911; Hirschhorn and Mulinos, 1930); but the results are too variable to be conclusive.

Digestive Tract.—Internally, mustard is used as a *condiment;* larger doses (1 to 4 teaspoonfuls of powdered mustard in a tumbler of warm water) produce *vomiting;* still larger doses cause violent gastro-intestinal irritation. *White mustard seeds* (Sinapis Alba) have a cathartic action, due to the liberation of H_2S on contact with water. Large doses may produce sulfide poisoning, with cyanosis, etc. (van Leersum, 1916). It may be used as emetic similarly to black mustard. Plants containing mustard oil (*Bursa pastoris*) stimulate the contractions of the excised uterus (Groeber, 1915).

ONION AND GARLIC

Plants of the genus Allium owe their odor, flavor and irritant action to volatile oils containing organic sulfides and allyl aldehyde. Their effects are similar to those of mustard. They were used in folk-medicine as counterirritants, especially in pneumonia.

Systemic Actions.—Oral administration of extracts of onion or garlic lower the *blood sugar level* of rabbits (Laland and Havrevold, 1933). *Smooth muscle* responds with brief stimulation, followed by depression (Lio and Agnoli, 1927). The effects on *frog heart* have been studied by Agnoli and Lio, 1927. Garlic vapor is somewhat *bactericidal*, due to its allyl aldehyde (Vollrath *et al.*, 1937).

The persistent odor of garlic in the expired air is due partly to fragments adhering to the structures of the mouth (Haggard and Greenberg, 1935), but chiefly to the pulmonary excretion of the absorbed sulfides which circulate in the blood stream (Blankenhorn and Richards, 1936). A mouthwash of chloramine (0.3 Gm. in 30 cc. of water) destroys the odor arising from the mouth, but not that from the lungs. A similar odor is conferred by tellurium and some arsenical compounds. *Milk of cows which have eaten wild garlic* is tainted with garlic odor. This is due partly to pulmonary absorption of the volatile oil (Babcock, 1925).

Thiosinamine, *allyl-sulfocarbamide*, was introduced by Hebra and Unna, 1892, and has been credited with causing the absorption of exudates, lymphatic swellings, scar tissue, etc.; and with the cure of lupus. It is usually administered by hypodermic injection (which need not be made at the site of the lesion) (Mendel, 1905). The administration must be continued for weeks and combined with massage and other adjuvant measures. It is therefore difficult to judge whether it has any value. It probably does little if any good, and it may produce toxic systemic effects, although it is usually well borne, except for the bitter taste and garlic eructations. Thiosinamine has been injected intravenously in arsphenamine dermatitis, in place of sodium thiosulfate (Greenbaum, 1924), but has not found favor.

Toxic Effects.—In man, 1 Gm., or 0.2 Gm. on repeated use, have caused headache, nausea, vomiting, lassitude and fever (J.A.M.A., *56:* 835, 1911; Charteris, 1910). These may set in suddenly after it has been used for a time uneventfully. In animals, Tyrode, 1909, found impaired respiration, eventually cessation and death, sometimes pulmonary edema and hyperemia (Lange, 1892). The circulation is not affected in mammals, but high concentrations paralyze the frog's heart. Smaller doses produce severe changes in metabolism, with loss of nitrogen and rapid emaciation; and fatty degeneration of parenchymatous organs, especially the heart and kidneys. Normal connective tissue showed no changes.

Other Allyl Compounds.—Allyl acetic acid, allyl urea and dimethylallylamine are indifferent; allyl iodide is strongly irritant; allyl formate produces necrosis of the liver and kidneys; allyl amine is highly toxic (Piazza, 1915).

OIL OF TURPENTINE

This produces simple reddening and burning when applied to the skin, is used as a counterirritant; undiluted, or mixed with 1 to 5 parts of oil in liniments. It is often employed as "stupe," *i. e.*, flannel wrung out of hot water, and then out of turpentine, and applied for ten to thirty minutes. In susceptible individuals it may cause severe eruptions and blistering if left on for several hours, but this is exceptional. Few painters develop dermatitis even from its daily use to cleanse the hands, if this is followed by soap and water. Hypersensitiveness may appear after many years of safe handling (L. Schwartz, 1939). Oil of turpentine is *used externally* in bronchitis, neuralgic and rheumatic pains, and to telieve meteorism. It causes more severe irritation on mucous membranes.

Inhaled or taken internally, it diminishes bronchial secretions (Rossbach and Fleischmann). It was used for this purpose (a teaspoonful inhaled from a pint of hot water) in chronic bronchitis, but has been displaced by the more pleasant terpin hydrate by mouth, and pineneedle or eucalyptus oil for inhalation. For the relief of *flatulence*, half to one teaspoonful of oil of turpentine, emulsified with the yolk of an egg, may be added to a soapsuds enema. Its use as anthelmintic (2 to 15 cc. followed by a saline purge) and as diuretic and urinary antiseptic have also been discontinued.

Various "expectorant" volatile oils increase the output of respiratory tract fluid when administered to animals by stomach tube, 50 mg. per Kg. (E. M. Boyd and Pearson, 1946).

Turpentine Abscess.—The injection of oil of turpentine produces localized aseptic abscess.

Absorption, Fate and Excretion.—Oil of turpentine is readily absorbed from the skin, lungs and intestines. It circulates for a time unchanged in the blood, and is excreted mainly in the urine as terpenals, paired with glycuronic acid. The urine has the odor of violets. Neither turpentine, nor eucalyptol nor menthol is excreted by the lungs or sputum (Falk, Hofbauer, 1915).

Systemic actions do not occur with small doses.

Toxicology.—Turpentine oil is easily accessible from its use in paints and varnishes and may give rise to accidental poisoning or be taken as abortifacient. Half an ounce has been fatal to children, 6 ounces to adults. The symptoms in man are those of gastro-intestinal irritation; nausea and vomiting, colic and diarrhea, wild excitement and delirium, ataxia, painful micturition, hematuria, albuminuria, glycosuria, skin eruptions, coma. The *treatment* comprises evacuation, demulcents and coffee.

Inhalation.—Fatal poisoning has been reported from inhalation of varnish in a confined space (Drescher, 1906), largely by exclusion of air (Wolf, 1911). There are rapid breathing, palpitations, vertigo, stupor, convulsions and other nervous disturbances; pain in the chest, bronchitis and nephritis. The latter may also occur on chronic exposure.

PREPARATIONS.—*Oil of Turpentine*, U.S.P. (Spirits of Turpentine), is the volatile oil distilled from the oleoresin (Turpentine) of various pine species. Distillation of this oil over sodium hydroxide yields ***Rectified Oil of Turpentine,** U.S.P. It consists chiefly of pinene and is the preparation for internal use. A thin, colorless liquid of characteristic odor and taste; practically insol. in water, sol. in 5 vol. of alc., and in all proportions of oils. Dose, 0.3 cc., 5 minims; as anthelmintic, 8 to 16 cc., 2 to 4 drachms, B.P. The U.S.P. *Emulsion* contains 15 per cent. Dose, 2 cc.

Terpin hydrate is used to diminish cough and expectoration in phthisis and chronic bronchitis, acting similarly to oil of turpentine, but is less irritant, less disagreeable and less toxic. It is sometimes employed as diuretic and urinary antiseptic, but is not very effective.

Lepine, 1887, claimed a diuretic effect from 0.2 to 0.4 Gm. Matzel, 1905, took 4 Gm. daily without any effect; the urine was not albuminous. It was excreted as paired glycuronic acid.

PREPARATIONS.—*Terpin Hydrate*, U.S.P. (Terpini Hydras), is prepared by hydrating oil of turpentine with alc. and nitric acid. Colorless crystalline powder, odorless, slightly arom. and bitter taste; sparingly sol. in water (1:200), sol. in alc. (1:13). Dose, 0.25 Gm., 4 grains, in powders and capsules. The *Terpin Hydrate Elixir*, N.F., contains 1 grain to the drachm. **Terebene** consists of dipentene and other terpene hydrocarbons, obtained by the action of sulfuric acid on oil of turpentine. Colorless, thin liquid of agreeable arom. odor and terebinthinate taste. Slightly sol. in water, sol. in alc. (1:3). Dose, 0.25 cc., 4 minims, on sugar or by inhalation.

Pine Needle Oil, U.S.P. (Ol. Pini Pumilionis; Oil of Dwarf Pine Needles), resembles oil of turpentine, but has a more agreeable odor, and is employed as an inhalant in bronchial affections. Steam distilled from fresh leaves of Pinus montana (Abies sibirica, Siberian Fir, Oleum Abietis, B.P.), a colorless or faintly yellow volatile oil.

EUCALYPTOL

Eucalyptol (Cineol, Cajeputol) is obtained chiefly from oil of eucalyptus, but occurs also in other volatile oils, such as cajuput. It is a mild local irritant, used especially in bronchitis, as inhalation (teaspoonful in hot water), or internally (5 to 10 drops on sugar); and in coryza (spraying with 3 to 5 per cent solution in liquid petrolatum). The oil of eucalyptus may be substituted. "*Nose drops,*" *i. e.*, solutions in olive oil or liquid petrolatum for instillation into the nares, should not contain more than 1 per cent of eucalyptol or camphor, or 0.3 per cent of menthol or thymol. Their prolonged use may lead to lipid pneumonia.

Toxicity.—Large doses of eucalyptol or the related *myrtol* produce excitement, rapid pulse, nausea, vomiting, dilatation of the pupils and fatal collapse. Death occurred in about one-third of the human subjects who had taken between 10 and 30 cc. Idiosyncrasy toward small doses is manifested by skin eruptions (L. F. Barker and Rowntree, 1918; experimental and clinical bibliography).

***Eucalyptus Oil,** U.S.P., is a colorless or pale yellow vol. oil steam distilled from the fresh leaves of Eucalyptus species, yielding not less than 70 per cent of eucalyptol. *Eucalyptol*, U.S.P., is a colorless liquid, sol. in alc. and oils, and practically insol. in water. Dose, 0.3 cc., 5 minims. *Cajuput Oil* is distilled from the fresh leaves and twigs of Melaleuca leucadendron. It is used mainly as a counterirritant.

RUBEFACIENT VOLATILE OILS

Many drugs containing volatile oils have been used as ingredients of liniments. With some of the tinctures (arnica, witch hazel) used in domestic medicine, the alcohol is perhaps the main active ingredient. Thymol, menthol, camphor and some of the volatile oils that are discussed in other connections could be classed with the rubefacients. The oils of clove, cinnamon and creosote are employed in *dentistry* to destroy the nerves and disinfect the cavities of carious teeth and to deaden the pain of toothache, a small drop of clove oil being introduced in the cavity.

Skin Pigmentation by Perfume Oils.—Oils of bergamot and of cedrus produce local sensitization of the skin to the actinic rays of the sun, resulting in irritation and pigmentation after the use of perfume ("cologne"), which contains these oils (del Vivo, 1930; Szanto, 1929). Tar causes similar sensitization (Herxheimer and Nathan, 1917). *Citrus fruit oils* in general are very irritant to the skin, due chiefly to the terpene, d-limonene, of which they contain about 90 per cent.

Liniments.—Cutaneous irritants are usually employed in the form of liniments, *i. e.*, in solution or suspension in oil or alcohol. The proportions in which they are used are about the following—20 per cent: Ammonia Water; Tr. Aconite, Belladonna, Iodine or Opium; Spirits Camphor, Chloroform or Ether; 10 per cent: Tr. Cantharides or Capsicum; Turpentine Oil; Sp. Sinapis; Essential Oils.

Clove Oil, U.S.P. (Oleum Caryophylli), is distilled from *Cloves*, U.S.P., the dried flower buds of Eugenia caryophyllata. It contains not less than 82 per cent of *Eugenol*, U.S.P., an unsaturated aromatic phenol obtained from oil of cloves and other sources. Dose, 0.1 cc., 1½ minims. Similar counterirritant properties are exerted by the volatile oils of *Amber*, *Cedarwood*, *Origanum*, *Pimenta* (Allspice), *Rosemary*, *Sassafras* and *Thyme*.

Arnica consists of the dried flower heads of Arnica montana and contains a volatile oil. Used externally; intravenous injections tend to produce lasting rise of blood pressure (E. D. Brown *et al.*, 1918). *Hamamelis Water* ("Witch Hazel Extract") is a saturated aqueous distillate from the twigs and leaves of Hamamelis virginiana to which about 15 per cent alcohol is added.

BALSAMS AND AROMATIC RESINS

Balsams (Peru, benzoin, tolu, storax) are oleoresins containing cinnamic and benzoic acids. The oils are antiseptic; the oils and resins, mildly irritant, stimulating repair; the resins furnish local protection and so allay inflammation. The balsams are applied in chronic inflammations of mucous membranes (bronchitis) and of the skin (eczema and pruritus); and to promote the healing of ulcers and wounds. Myrrh acts similarly. The balsams are also used locally against scabies, destroying the acarus and their ova. Peru balsam is employed locally and internally for tuberculosis (for intravenous use, see "Cinnamic Acid"). Its internal administration is of doubtful utility, as is also the internal use of other balsams in bronchitis. Even large doses of the balsams do not produce albuminuria (Stockman, 1890).

Benzoin, U.S.P. (Gum Benjamin), is a balsamic resin obtained from Styrax Benzoin (Sumatra Benzoin), S. tonkinensis and other species of Siam Benzoin. The *Tincture,* U.S.P., contains 20 per cent. The ***Compound Tincture of Benzoin,** U.S.P. (Tr. Benzoini Composita; Friars' Balsam, Turlington's Balsam), is representative of the old "balsamic tinctures." It contains benzoin (10 per cent), aloe, storax and tolu in alcohol. Dose, 2 to 4 cc., ½ to 1 drachm, as stimulant expectorant; as inhalant, teaspoonful to cup of boiling water; externally, mixed with glycerin or water, as lotion for chapped hands. The original formula was much more complex; the present formula is still needlessly complicated and expensive. When used as inhalant, the steam contains a trace of oil and benzoic acid (Peacock and Deg, 1919), which would be deposited on the mucous membranes. The same results would probably be secured more simply by substituting the official Tr. Balsam. Tolu.

Peruvian Balsam, U.S.P., is obtained from Toluifera Pereirae. Dark brown, viscid liquid of agreeable vanilla odor; freely sol. in alc. Externally on lint; in scabies, inunction of 2 to 3 Gm., four to six times a day; as a stimulant in indolent ulcers and bed sores, diluted with two parts of castor oil. It is said to promote healing without stimulating granulation; but it is sometimes irritating. It prevents adherence of dressings, but leaves an indelible stain on fabrics. The odor may become objectionable on continued use. *Storax,* U.S.P. (Styrax), is a similar balsam. Dose, 1 Gm. (0.6 to 2 Gm.), 15 grains (10 to 30 grains), in bronchitis. *Tolu Balsam,* U.S.P. (Balsamum Tolutanum), obtained from Toluifera Balsamum, has a pleasing odor resembling vanilla. The *Syrup,* U.S.P., is used as a vehicle.

Myrrh, U.S.P. (Myrrha), a gum resin from Commiphora species, was used by the ancients as incense in religious ceremonies, and by the Egyptians in embalming, in combination with spices. The *Tincture,* U.S.P., 20 per cent, is carminative (dose, 1 cc., 15 minims); it is used especially as a mouth wash (1:25) in stomatitis, pharyngitis, and as a lotion 1:5 or 10. *Mastic* (Mastiche) is a similar resinous exudation from Pistacia Lentiscus. *Mastic Varnishes* have been used in surgery to fix the skin bacteria on the hands and operative area. They are brushed on and allowed to dry. The skin may first be treated with iodine. Various formulae have been published; Borchardt's consists of mastic, 40 Gm.; benzene, 60 Gm.; castor oil, 20 drops, filter. *Galbanum* is a gum resin from Ferula galbaniflua.

Echinacea, the root of Echinacea angustifolia (Purple Cone Flower), contains resins and no alkaloids (Heyl and Staley, 1914). Several proprietary preparations have been praised for sialagogue, diaphoretic, stimulant and general alterative effects; but no good evidence of its value has been published and the claims appear extravagant (J.A.M.A., Nov. 27, 1909). Dose, 1 to 2 Gm., 15 to 30 grains. *Grindelia,* the dried leaves and flowering tops of Grindelia camporum, contains an amorphous resin (probably the active principle) and a very small quantity of volatile oil, no saponin or alkaloid (Power and Tutin, 1905). It is said to relax the muscular coats of the bronchi and diminish the excretion of mucus. It is therefore used in asthma and bronchitis. *Pellitory* (*Pyrethri Radix*), the root of Anacyclus pyrethrum, is chewed as a sialagogue and against tootache.

DIURETIC VOLATILE OILS

Volatile oils tend to increase the urine flow by irritating the kidneys. Larger doses produce nephritis and anuria. Turpentine and juniper oil were used as diuretics, but the possibility of harmful irritation has restricted their employment.

The oxygen consumption of the kidneys is increased by turpentine or sandalwood oil, regardless of whether there is diuresis (Kaburaki, 1927). These oils also produce histologic abnormalities of the renal epithelium (Tukioka, 1927).

Juniper Oil, U.S.P., is distilled from the ripe fruit of Juniperus communis. It is closely allied to turpentine (containing pinene, $C_{10}H_{16}$, and cadinene, $C_{15}H_{24}$); but it has a more agreeable flavor. In the form of "*Holland Gin,*" it was employed as diuretic (Cow, 1912) in cardiac and hepatic dropsies. It is supposed to act by mild irritation of the kidneys. Its use in nephritis requires caution It also had some reputation as emmenagogue. Overdoses produce poisoning, similar to savin (see below).

VOLATILE OILS AND OLEORESINS EMPLOYED IN URETHRITIS AND CYSTITIS

Oil of Sandalwood and the oleoresins of Copaiba, Cubeb and Matico were administered as urinary antiseptics in subacute and chronic urethritis, as adjuvants to local treatment, to diminish the pain and the discharge, and to hasten healing, but they are not curative. Their use has greatly diminished, as the beneficial results appear too uncertain to offset the side effects. Santal oil is generally preferred. It is best administered in capsules, on a full stomach, to minimize gastric irritation. Buchu is used as a diuretic in catarrhal cystitis; cubeb is sometimes employed in bronchitis.

The oleoresins are natural mixtures of resins and volatile oils rich in terpenes and terpene alcohols. The terpenes are excreted as glycuronic compounds, which have a slight antiseptic action on the urine. This is much less than that of methenamine, but it has the advantage that it is not affected by the reaction of the urine (Jordan, 1911); probably they are specifically more effective for certain bacteria. The gonococci are not killed (Bruck, 1913), but the control of the putrefactive bacteria presumably puts the mucous membrane in a better position for resistance. The terpenes and resin acids are mildly irritant. The urinary passages are thus kept under the continuous influence of the antiseptic terpenes, and stimulated to repair by the irritation. Winternitz, 1901, and Pohl, 1912, found that the oral administration of various balsams, santal oil, etc., appeared to have favorable effects on *experimental aseptic pleurisy* (aleuronat, etc.) in rabbits. However, their doses were much larger than the clinical.

Side Actions.—The gastro-intestinal tract is also irritated, resulting in anorexia, colic, eructations and diarrhea. These unpleasant effects are less with santal oil, and may be minimized by the use of the santalol esters, which are only dissolved in the intestines. Skin eruptions, scarlatinal rashes, etc., occur in some patients, either directly or from the digestive disturbance. Excessive doses of the oils produce more pronounced irritation of the entire urinary tract, with kidney pain, albuminuria and vesical tenesmus. Albuminuria may be simulated by the precipitation of the resin acids with nitric acid: to be distinguished by the addition of alcohol, which dissolves the resins. Glycosuria may also be simulated by the glycuronic acid.

Santal Oil, N.F. (Ol. Santali; Sandalwood Oil), is distilled from the heartwood of Santalum album; a pale yellow, viscid, oily liquid; peculiar aromatic odor, spicy taste; sol. in alc. It often disturbs the stomach, and sometimes causes vesical and renal irritation. Dose, 0.3 to 1 cc., 5 to 15 minims. It consists chiefly of *santalol,* a mixture of two sesquiterpene alcohols.

Copaiba, N.F. (Balsam of Copaiba), is an oleoresin obtained from South America species of Copaiba. A pale yellow or brownish yellow, viscid liquid; peculiar aromatic odor and persistent, bitter acrid taste; insol. in water, partly sol. in alc., freely sol. in oils. Dose, 1 cc., 15 minims. The various "Lafayette," "Chapman" and similar mixtures are undesirable.

Cubeb Oleoresin is an evaporated alcoholic extract of the dried, full grown, unripe fruits of Piper Cubeba. Dose, 0.5 Gm., 8 grains. *Matico* consists of the leaves of Piper angustifolium. *Buchu* is the dried leaves of various species of Barosma. Contains vol. oil, glucoside, bitter principle, etc.; best as infusion.

Sabal (Saw Palmetto) is the partially dried, ripe fruit of Serenoa serrulata. Statements as to presence of alkaloids and vol. oils are contradictory. Has been used as nutritive tonic, alterative, in respiratory diseases, digestive disturbances, as aphrodisiac, etc. Of doubtful value. Dose, 1 Gm., 15 grains.

ECBOLIC AND TOXIC VOLATILE OILS

Several volatile oils are employed in folk medicine as emmenagogues and ecbolics; especially apiol, savin, pennyroyal, tansy, rue, turpentine and juniper. They may produce pelvic congestion through intestinal irritation. A mild degree of this action was supposed to be useful in delayed and painful menstruation, as after exposure to cold, but it is doubtful whether safe doses are effective. Abortion occurs only with toxic doses (Datnow, 1928); indeed, fatal doses are not always ecbolic. Fatty degeneration of the liver and other organs results from large doses of these oils, especially from pennyroyal (pulegone), and also from nutmeg, sassafras, rosemary and thyme (Heffter, 1895; Lindemann, 1899).

Excised uterus gives variable responses to the different drugs. Prochnow, 1911, reported slight stimulation; Macht, 1913, invariably obtained depression. Apiol appears to be somewhat stimulant (see below). Excised human uterus is not stimulated by the oils of juniper, pennyroyal, rice, savin or tansy. Low concentrations have no effect; active doses produce relaxation and inhibition (Gunn, 1921).

Apiol.—Two drugs are known under this name: "Green Apiol," or Oleoresin of Parsley Seed, a green oily liquid; dose, 0.3 to 1 cc., 5 to 15 minims; and "Apiol" proper, "Crystallized Apiol," "Parsley Camphor," a crystalline aromatic derivative extracted from the oleoresin; dose, 0.1 to 0.3 Gm., 2 to 5 grains. The apiols are administered in capsules, as emmenagogue and antipyretic. Their usefulness is doubtful. Overdoses produce arrhythmia, incoordination, digestive disturbances and fever. Fatal poisoning with intestinal irritation, icterus and uremia was reported by Brenot, 1916. Dogs and rabbits poisoned with apiol and related drugs show visceral fatty degenerative lesions, especially in the liver and kidneys. Individual tolerance varies widely. Excised uterus, intestines and ganglion-free leech muscle are stimulated (Heffter, 1895; Patoir *et al.,* 1935; Lutz, 1920). Adulteration of green apiol with ortho tricresyl phosphate (see Index) has given rise to serious neuritis.

Savin (*Sabina*) and **Arbor Vitae** (*Thuja*) contain volatile oils (Cedar Leaf Oil, U.S.P.) similar to turpentine but much more toxic. Thuja contains pinene, fenchon and thujone (isomers of camphor, having similar actions) (Hildebrandt, 1902; Matzel, 1905). Poisoning has often occurred from their use as abortifacients. Six drops of oil of savin are said to have produced toxic effects: burning, nausea, vomiting, colic and diarrhea, sometimes bloody; severe congestion of the pelvic organs, increased menstrual flow and sometimes abortion; hematuria and painful micturition; unconsciousness, convulsions and coma. Death may occur in a few hours, but more often after several days (Lewin). The chief effect in animals is intestinal irritation (Kagaya, 1927).

Tansy.—The leaves and tops of Tanacetum vulgare have been used as anthelmintic against Ascaris and Oxyuris, internally, 0.5 to 2.5 Gm. as infusion, twice a day; or as enema of 15:200. Half an ounce to an ounce of the oil (which contains thujon) has produced death after two to four hours, with convulsions and unconsciousness.

Pennyroyal.—The leaves and tops of Hedeoma pulegioides are used as carminative, 5 to 10 Gm., 1 to 2 ounces, as infusion. *Ol. Hedeomae,* 0.2 cc., 3 minims; a teaspoonful has produced convulsions. Its active constituent, *pulegone,* has been studied by Matzel, 1905.

Nutmeg Poisoning.—In man severe symptoms have occurred from one to one and one-half nutmegs, or from a teaspoonful of powdered mace. The effects appear in one to six hours, and are mainly narcotic, varied by excitement and delirium, with some motor stimulation and local irritation; they usually end in recovery in twenty-four hours. Nutmeg is also ecbolic. Similar effects occur in animals. Hepatic necrosis has been demonstrated in cats (Dale, 1909). Cushny and Wallace, 1908, showed that the narcotic effect is produced by "*myristicin*," the high boiling portion of the volatile oil. The oil has been investigated chemically by Power and Salway, 1908. *Myristica*, U.S.P. (Nutmeg), is the ripe seeds of Myristica fragrans. Dose, 0.3 to 0.6 Gm., 5 to 10 grains. The dose of Myristica Oil, U.S.P., is 0.06 to 0.2 cc., 1 to 3 minims.

Senecio.—The alkaloids (*senecine, senicionine, seneciophylline, riddeline* and others) of S. Jacobea and vulgaris and other species produce toxic effects in cattle resembling those of volatile oils; hemorrhages in abdominal organs, especially the liver; fatty change, necrosis, congestion and hepatic cirrhosis, leading to ascites and terminating in coma (Cushny, 1911). Prothrombine time is prolonged, but may be restored by feeding of vitamin K (C. L. Rose *et al.*, 1945). The primary effect appears to be vascular (J. Davidson, 1935). The renal tubules and glomeruli are also injured. Intravenous injection of the alkaloids causes rise of blood pressure, convulsions, uterine contractions and intestinal relaxation. Excised intestine is relaxed; uterus of guinea pigs and rabbits is contracted. Another senecio alkaloid, *platyphylline*, when injected by vein, causes convulsions, probably medullary, but no renal or hepatic damage (Chen *et al.*, 1940; Harris *et al.*, 1943). *Lasiocarpine*, the alkaloid of a *heliotrope*, has similar effects (K. K. Chen, Harris and Rose, 1939). The fluidextract of senecio (10 to 20 drops) has been used as emmenagogue. It has a slight depressant effect on the excised uterus (Pilcher, 1916).

Helenium autumnale contains a neutral bitter principle (Reeb, 1910) which is strongly irritant to mucous membranes. Systemically, it stimulates respiration and directly paralyzes cardiac and other muscle. It is not hemolytic (Lamson, 1913).

Spewing sickness, a sheep disease of Utah, is due to the eating of *Dugaldia* hoopesii, a composite plant allied to Helenium and probably containing similar active principles. It produces similar gastro-intestinal and cardiac symptoms (D. D. Marsh, 1916).

Eupatorium Urticifolium (*Ageratoides*).—Feeding on the green plant is said to be the cause of one form of "trembles" or "milk sickness" of sheep; the symptoms consist in weakness and ataxia, ending in death (Marsh and Clawson, 1917). The toxic principle is extracted by 95 per cent alcohol (Sackett, 1919). *Other species of Eupatorium* (Boneset) are used as diaphoretic tea.

Hypericum.—Ray, 1914, stated that cattle feeding on a Tunisian species (H. crispum) develop dermatitis of nonpigmented portions of the skin, and inflammation of the mucous membranes exposed to light. The phenomena are due to a *fluorescent substance*. Rogers, 1914, claims analogous effects for the common St. John's wort, Hypericum perforatum.

Buckweat Photosensitization.—Feeding with the flowers or seedhusks or hay of buckwheat (Fagopyrum esculentum) renders guinea pigs, white rats and mice sensitive to light of wave lengths 540 to 610, resulting in the syndrome of *fagopyrism:* inflammation of the skin, especially about the eyes, ears, nose and tail, and of mucous membranes (conjunctivitis, diarrhea); and convulsions. With a single dose of 0.25 Gm. per 100 Gm. the effects occur in twenty-four hours and persist some days (Chick and Ellinger, 1941). Photosensitization by handling of *parsnips* has been reported (V. Starck, 1944),

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GASEOUS IRRITANTS AND "WAR GASES"

Irritant gases are important chiefly as industrial poisons and in chemical warfare. The former include ammonia, chlorine, bromine, the fuming mineral acids, the gaseous acids, such as sulfurous, nitrous, etc.; the volatile organic acids—acetic, formic, etc., and formaldehyde. *Warfare "Gases"* include not only true gases and liquids with sufficiently high vapor tension, but all other forms that may be diffused through the air as smokes, sprays and dusts, by the heat or force of the explosion of the shell.

Available Substances.—Practically every substance of sufficient toxicity and heat stability may thus become an implement of "gas warfare." The choice of the substances is limited by the fact that they must be effective even when highly diluted. In practice, this requirement is best met by irritants. Curiously, it has excluded hydrocyanic acid, arsine, phosphine and hydrogen sulfide, substances that owe their sinister reputation mainly to rapidity of action, but which apparently can not be used with sufficient concentration in ordinary military operations. Dense liquids and solids have an advantage in that they are not so rapidly dissipated by the wind.

The military effectiveness of poison gas is due to the morbidity rather than to the mortality; 98.3 per cent of the gas casualties of the first World War recovered completely. Popular ideas of fatalities do not correspond to field conditions (A. L. Kibler, 1935). In a confined space a man could probably be killed by 20 mg. of mustard gas; in the war, however, one and one-half tons were expended for each fatality, and seventy-five pounds for every casualty (G. E. Miller, 1937). Hysterical manifestations, such as persistent vomiting, aphonia, blepharospasm, and other psychosomatic reactions are more common sequels than physical disabilities (Rennie and Small, 1943). The experiences of the war are described in "Vol. XIV, Medical Aspects of Gas Warfare," of "The Medical Dept. of the U. S. Army in the World War," 1926. War gases offer some danger of *accidental water contamination*, especially by the arsenical smokes and, to some extent, mustard gas; phosgene does not. In any case, water contamination can be fairly easily prevented or removed.

Classification of Substances Used in Chemical Warfare.—These may be grouped, chiefly by the usual location of the irritation, as (*a*) *pulmonary irritants*, chlorine, phosgene, palite, chloropicrin (nitric vapors, sulfur dioxide and ammonia belong to this class, but are not used in warfare); (*b*) *vesicants*, mustard gas and Lewisite; (*c*) *lachrymators* ("tear gases"), often contain halogen groups. The most important are chloroacetophenone and brombenzylcyanide; (*d*) *irritant smokes*, chiefly diphenylamine chlorarsine and diphenyl chlorarsine (G. E. Miller, 1937). The actions are not sharply localized, but differ according to circumstances, especially the concentration and duration of exposure. However, the effects adhere pretty closely to the type classification under ordinary conditions.

Other purposes of warfare served with relatively nontoxic agents are (*e*) *screening smokes*, titanium tetrachloride, chlorsulfonic acid, sulfur trioxide, white phosphorus; (*f*) *incendiary agents*, white phosphorus, thermite, solidified oils.

Effective Concentrations of Irritant Gases.—The following data, adapted from Henderson and Haggard's "Noxious Gases," expressed as parts per million (by volume) of air, apply to man. They are arranged in descending sequence: *Lowest concentration detectable by odor:* NH_3 = 53; $COCl_2$ = 5.6; SO_2 = 3 to 5; Cl = 3.5. *Lowest concentration producing immediate irritation of the eyes:* NH_3 = 698; SO_2 = 20; $COCl_2$ = 4.0. *Lowest concentration producing immediate irritation of the throat:* NH_3 = 408; NO_2 = 62; Cl = SO_2 = 8 to 12; $COCl_2$ = 3.1. *Least concentration for coughing:* NH_3 = 1720; NO_2 = 101; Cl = 30; SO_2 = 20; $COCl_2$ = 5. (In general, it requires about one and one-half times as much to irritate the eyes, and about twice as much to produce coughing, as suffices to irritate the throat.) *Maximal concentration allowable for prolonged exposure:* NH_3 = 100; NO_2 = 39; HCl and SO_2 = 10; HF = 3; Cl and $COCl_2$ = 1; *maximum allowable for one-half to one hour exposure:* NH_3 = 300 to 500; NO_2 = 115 to 155; SO_2 = 50 to 100; HCl = 50; HF = 10; Cl = 4. *Dangerous even within half an hour:* NH_3 = 2500 to 4500; HCl = 1000 to 2000; NO_2 = 240 to 775; SO_2 = 400 to 500; HF = 50 to 250; Cl = 40 to 60; $COCl_2$ = 25. *Rapidly fatal with short exposure:* NH_3 = 5000 to 6000; Cl = 1000; $COCl_2$ = more than 25. (In general, the concentrations allowable for an hour are about four times, and those dangerous within half an hour are about fifty times, the maximum allowable for prolonged exposure.)

The concentration ppm by volume (at 25° C., 760 mm. pressure) **may be transposed** to mg. per liter by multiplying by the molecular weight and dividing by 24,450. Conversely, mg. per liter is transposed to ppm (vol.) by multiplying by 24,450 and dividing by the molecular weight.

The Phenomena of Gas Irritation.—When swallowed, the volatile irritants produce the ordinary phenomena of gastro-intestinal irritation. When inhaled, they irritate the respiratory passages and other exposed mucous membranes, causing conjunctivitis, rhinitis, bronchitis, pulmonary edema and pneumonia. The phenomena are essential uniform for man and other mammals, for all volatile irritants, but differ in the relative intensity of the effects on the upper and deeper respiratory passages, and in the sensory irritation and reflexes, which arise only above the bronchioles. Generally, the more soluble gases act high, the less soluble gases prolong their action in the lungs; but there are exceptions. The gases that act directly, as does chlorine, also begin their effect in the pharynx; while those which act only after decomposition by moisture, such as phosgene and palite, cause chiefly alveolar irritation.

Ammonia, hydrochloric, sulfuric and hydrofluoric acid and formaldehyde act mainly on the *upper portion;* chlorine, bromine, sulfur dioxide, hydrogen sulfide and acrolein act on *all portions;* nitrous fumes, phosgene, ozone, phosphorus trichloride and pentachloride and arsenic trichloride act chiefly on the *alveoli.*

Acutely Lethal Concentrations.—Prompt death occurs especially with high concentrations of the direct irritants (for example, 1 to 5 per cent of **chlorine**), through reflex spasm or acute edema of the glottis, or by obstruction of the pulmonary irritation. The symptoms are those of violent respiratory irritation and rapid asphyxial syncope.

The experiments of Schaefer, 1915, showed that *1 per cent of chlorine* in the air may be ineffective for several minutes; then, often suddenly, the respiration becomes deep, convulsive and arrested. The blood pressure falls. Rapid recovery occurs in fresh air. With *5 per cent,* death is rapid and inevitable. The respiration becomes slowed and is arrested in one to three minutes. The blood pressure falls to zero in three to four minutes, the heart still beating well. Artificial respiration does not cause recovery. The *bronchioles* are not constricted, air passing at least as well as normally. Secretion of mucus is also unimportant, for the course is not modified by atropine. The *systemic circulation* is also unaffected directly, the changes being secondary to the asphyxia. Even the right heart is not especially congested.

The essential changes are in the *pulmonary circulation.* The lungs are intensly hyperemic, microscopic examination showing engorgement of the capillaries and edema of the intestinal tissue and alveoli. The epithelium proper is normal. Perfusion of the pulmonary vessels with Ringer's solution shows marked obstruction of the flow when chlorine is injected into the trachea or perfusion fluid. Schaefer assumed that this phenomenon occurs during life and that this obstruction is the cause of all the symptoms. (It is probable that chlorine coagulates the endothelium, as do other astringents.) **Bromine vapor is more irritant, but less fatal.**

Respiration.—Inhalation of high concentration of chlorine (admitted directly into the trachea) arrests the respiration completely, for twenty seconds or longer. This is followed by peculiar, abortive abdominal movements, and these by restoration of practically normal respiration. Further chlorine does not again arrest the respiration (Schultz, 1918). Inhalation of air containing chlorine 1:5000 to 1:1000 produces quickening of the respiration and transient broncho-constriction, due partly to edema of the bronchial mucosa (Azzi, 1918). There may also be a direct action on the bronchial musculature; for excised rings are strongly contracted when placed in Ringer's solution containing fairly high concentrations of chlorine. Low concentrations relax. Rings of *pulmonary artery and vein* behave similarly; but it is doubtful whether they are exposed sufficiently in life.

Heart.—In mammals, inhalation of concentrated chlorine often produces prompt temporary arrest of the heart. If the heart resumes, the pulse and respiration remain greatly slowed. These effects are absent if the vagi have been divided. The exposed frog or terrapin's heart and especially the mammalian heart are immediately depressed by chlorine in Ringer's fluid or in the air (Schultz, 1918).

Subacutely Toxic Concentrations of Volatile Irritants.—The greater number of accidental intoxications and practically all war gas casualties belong to this group. The distinguishing feature is the occurrence of profuse pulmonary edema. With direct irritants, this may be preceded and accompanied by sensory phenomena, reflexes and inflammation of the respiratory passages.

Most of the irritant gases are not absorbed as such from the lungs. They therefore do not have direct systemic actions. All their effects are explainable as direct or indirect results of the local irritation. The indirect effects are produced by asphyxia or by reflexes.

The fatigue and exhaustion of the mild cases and the loss of consciousness in severe cases are asphyxial. Retching and vomiting result from pharyngeal irritation and from the cough. Diarrhea is emotional. The kidneys are practically unaffected.

The results of the German experiments with war gases are described in the thirteenth volume of the Zeitschrift für die gesammte experimental Medizin.

Sensory phenomena and reflexes are conspicuous with direct irritants, such as chlorine; delayed or absent with the slower acting poisons (phosgene). They begin with the characteristic *odor* of the gas. Dogs with their keen scent note the presence of gas much earlier than does man, and run away from it. The *irritation* starts with the first two or three inspirations of the directly irritant gases; for instance, chlorine 1:1000 to 1:10,000, or with ammonia vapor, etc. There is a sensation of pain and choking, which causes a reflex temporary arrest of the respiration, in expiration, spasmodic closure of the glottis, and bronchial constriction and reflex inhibition of the heart. These are conservative reactions, which temporarily exclude the poisonous gas and prompt the subject to seek pure air. They explain why fatal effects are relatively rare; but if the respiratory arrest exceeds 70 to 80 seconds, the subjects generally do not recover (Fabroni, 1929). Excessive spasm or edema of the glottis may be directly fatal. The protection can only be temporary if exposure to the gas continues. The air hunger leads to dyspneic, spasmodic and painful respiration, resembling asthma, although the bronchi may not be constricted. Asthmatic individuals are indeed especially sensitive to direct respiratory irritants. There may be violent coughing, with frothy expectoration. Acute asphyxia develops, with cyanosis and great anxiety, then mental confusion and lethargy, and finally unconsciousness. Eventually the condition passes into pulmonary edema and circulatory collapse. These, rather than the immediate phenomena of irritation, are the fatal features of the intoxication (L. Lewin, 1908). The irritation also affects the conjunctiva, resulting in lachrymation and congestion. Swallowing of the irritant with the saliva may inflame the esophagus and stomach, with protracted hemorrhagic gastritis (Loper *et al.*, 1915).

Acute epithelial injury by gases increases progressively in inverse ratio to the robustness of the cells, from the trachea to the alveolar endothelium. The functional injury may be much greater than the histologic changes. In acute gas cases, particularly, severe edema may occur before the cells present any morphologic abnormalities.

Lesions of Upper Respiratory Tract.—Chlorine and other direct irritants, including "mustard gas," produce more or less violent inflammation of the larynx, trachea and bronchi. In case of survival these are likely to lead to secondary infections: laryngitis, tracheitis, bronchitis and lobular pneumonia. Those gases which liberate chlorine only on contact with water (phosgene, palite, superpalite, etc.) cause little or no inflammation of the upper respiratory tract. They are also somewhat less productive of secondary pneumonia.

Irritative pulmonary edema is the essential danger factor with all the volatile pulmonary irritants; its mechanism, phenomena and treatment being essentially the same for all.

Other Forms of Experimental Pulmonary Edema.—The methods employed, reviewed by Schlomovitz, 1920, may be arranged into the following groups:

1. Embolism of artery by fat, lycopodium, etc.; intravenous collargol. 2. Injury to pulmonary capillaries by excessive hydremia; excessive blood concentration and anoxemia. 3. Injury to pulmonary capillaries by intravenous acetic ether, or ammonia. 4. Injury to respiratory epithelium; irritant gases. 5. Clinical inflammatory type, mainly by vascular injury. 6. Disproportion in the work of the right and left ventricles; compression of the left ventricle (Welch); epinephrine injection; muscarine asphyxia. 7. Combinations.

The pre-edemic stage (*first stage of phosgene poisoning*) is characterized by congestion and stasis in the pulmonary circulation; dilatation of the right heart, dilution and increased volume of the blood.

Thrombosis of the pulmonary vessels is especially prominent in chlorine poisoning. Many of the pulmonary capillaries are occluded by agglutinated red cells. This process reaches its maximum rapidly, in one or two hours at the latest, and then gradually diminishes. The thrombosis may be partly the result of the usual inflammatory stasis; but probably is largely due to the direct action of the acid gases on the blood corpuscles; for agglutination may be produced *in vitro* by dilute chlorine, phosgene or hydrochloric acid.

The oxygen content of the blood decreases considerably, nearly parallel to the deficiency of the hemoglobin. This, together with the obstruction in the pulmonary circulation and the venous stasis, produces some asphyxia and dyspnea; but the respiratory symptoms in this stage of phosgene poisoning are not severe.

Chlorine poisoning is always accompanied by *acidosis*. In case of survival the blood recovers its normal values rapidly, often in a few hours. The alkali reserve of the tissues was therefore not seriously depleted. In fatal cases, however, the reserve alkali of the blood continues to fall progressively. This is of prognostic importance.

In *phosgene poisoning*, acidosis occurs only shortly before death; *i. e.*, there is only the terminal acidosis that is likely to precede death from any cause.

Stage of Pulmonary Edema (*Second Stage of Phosgene Poisoning*).—The pulmonary capillaries, which were irritated and obstructed in the first stage, become gradually permeable, leading to pulmonary edema. Heubner, 1919, believes that the pulmonary stasis plays a greater part than the direct irritation of the endothelium. The edema results in diminished blood volume, concentration of the hemoglobin and decreased size of the heart. This is liable to develop quite rapidly, especially in chlorine poisoning, and may reach extreme degrees. Most of the fatalities occur in this stage, from anoxemia and decreased blood volume (Meek and Eyster, 1920).

Blood concentration, with increase of blood count, hemoglobin and viscosity, occurs rapidly with chlorine, slowly with phosgene, reaching its maximum about the fifth to eighth hour. It may then remain stationary for some time. The rapidity and degree of the concentration are proportioned to the severity of the intoxication and are therefore of prognostic importance.

Circulatory Collapse.—Severely gassed patients suffer more or less from circulatory collapse, as shown by a gray pallor, by rapid and feeble pulse and by venous congestion and dilatation of the right heart (never of the left). The collapse is often the immediate cause of death. The circulatory collapse is due mainly to the asphyxia, but is aided by the local conditions in the lungs, by the increased viscosity and thrombosis, and by the compression of the capillaries and veins through the edema.

Development of the Pulmonary Edema.—The fluid exudes first into the air sacs and from there overflows into the bronchioles and bronchi. Here it is churned into foam by the tidal air. As this foam mounts toward the larger air tubes, it provokes the cough reflex, and is more or less effectively expelled, until the exudate and foam become so excessive that they produce fatal asphyxia. The edema compresses the pulmonary capillaries, another factor in the impeded pulmonary circulation. Some of the exudate may also form in the pleural cavity, but usually in scanty amount.

Respiration.—The minute-volume of respiration is always increased after the symptoms of gassing develop. With chlorine, the sensory phenomena dominate the respiration. With phosgene, the increase of respiration is asphyxial and therefore increases with the edemal stage.

Disruptive emphysema is especially serious in *chlorine* gassing because of the violent coughing and inspiratory efforts provoked by the irritation of the gas. These efforts tend to tear the partitions between the alveoli. The pulmonary tissue may be ruptured so extensively that air escapes even into the subcutaneous tissue of the neck. The much milder sensory irritation of *phosgene* poisoning leads to less violent muscular efforts, and emphysema is therefore less prominent. Disruptive emphysema diminishes permanently the breathing area, so that survived piatients are apt to suffer indefinitely from shortness of breath.

Gas Exchange in Irritative Pulmonary Edema.—In chlorine poisoning, air hunger sets in rapidly, but soldiers gassed with phosgene do not complain of air hunger for some time, although they may show intense grayish cyanosis and may even die. This is a condition of anoxemia analogous to mountain sickness. If the patient survives, the cyanosis gradually changes to the ordinary blue tint, and he develops air hunger and intense hyperpnea. These are the phenomena of carbon dioxide poisoning. In other words, the patient passes first through a condition of pure anoxemia; this is then complicated by the accumulation of CO_2, which develops much more slowly.

Haldane explained the early dissociation of the oxygen and carbon dioxide factors of asphyxia by the relative solubility of the two gases. CO_2 is twenty-five times more soluble in water than is oxygen. Consequently, when the exudate begins to form, it interposes a much greater obstacle to the passage of oxygen than to the passage of CO_2. This would result in the anoxemia without carbon dioxide accumulation, as noted clinically. These conditions change, however, when the edema fills the alveoli, and its foam mounts more and more into the bronchioles and bronchi. When this happens, the air is totally prevented from reaching the alveoli. The respiratory exchange stops in that part of the lung, and CO_2 accumulates. This produces more or less hyperpnea, and this in turn produces overventilation of functionating portions of the lung. Their CO_2 therefore falls below the normal level. The blood returning to the left heart is a mixture derived from the overventilated and the unventilated parts of the lung—the first with a deficiency of CO_2, the second with an excess of CO_2. These two factors tend to balance each other, so that the CO_2 excess of the mixed blood is not at first very great. It increases as more and more of the lung is thrown out of function. On the other hand, overventilation does not increase the oxygen of the blood anywhere, since the hemoglobin in the functional part of the lung is practically saturated with oxygen by ordinary ventilation. The overventilated portions of the lung do not compensate for the asphyxiated portions. The uncompensated oxygen deficit therefore continues greater than the more or less compensated CO_2 excess.

The administration of oxygen reverses these conditions: oxygen diffuses gradually through the foam, and thus the foam near the alveoli becomes so much enriched in oxygen that a sufficient quantity can diffuse into the alveolar exudate. The CO_2 excess is not lowered by this, so that oxygen inhalation abolishes the cyanosis and diminishes the danger of asphyxial death; but it does not diminish the hyperpnea. The air hunger, the amplitude and rate of respiration are not changed by the oxygen. Since the oxygen must diffuse through the foam before it can be effective, the relief is rather slow, coming on only after about five minutes. This contrasts with the instantaneous response to oxygen in ordinary obstructions.

Postmortem findings differ somewhat for chlorine and phosgene (Winternitz, 1919):

Chlorine Followed by Acute Death (Inside of Twenty-Four Hours).—The trachea and bronchi are red and congested, edematous and may be more or less filled with serous exudate. The lumen of the bronchioles may be filled with debris. The lungs are heavy and edematous with overdistended, emphysematous areas scattered through the purplish collapsed and depressed structures. On section, serous fluid flows abundantly.

Postmortem Findings for Phosgene.—When death has occurred within two hours after exposure, the lungs are uniformly edematous, airless and purple. There is little or no emphysema. The lungs exude abundant fluid on section. There is also considerable fluid in the pleural cavities. When death occurs later (second or third day), the pulmonary edema is less, the lung containing some aerated areas. This may be because all the cases of severe edema die early. However, it is conceivable that in nonfatal cases a reabsorption of the edema occurs from the second day, since even deeply cyanosed patients may ultimately recover.

The degree of the pulmonary edema may be determined post mortem by the water content of the lungs, or by the ratio of their weight to that of the heart.

Prognosis in the Edema Stage.—Experience with animals indicates that the severity of the intoxication and the direct fatality in phosgene poisoning may be judged with fair certainty by the course of the blood concentration and by the temperature. The more rapidly the blood concentration sets in, and the higher its degree, the more grave is the danger. The temperature does not change in light cases. In severe cases, there is a preliminary rise, followed by a later fall. This fall is rapid in fatal cases, gradual in those that survive.

Phenomena of Restoration (*Third Stage of Phosgene Poisoning*).—If the patient does not succumb to the pulmonary edema, the excessive concentration of the blood gradually disappears, so that it finally becomes slightly more dilute than normal. The edema is slowly reabsorbed; and there is a fairly rapid readjustment and eventual return to a practically normal condition. The stage of restoration is often complicated, however, by secondary respiratory infectional pneumonia or bronchitis, which may run a fatal course.

Late Effects of Irritant Gases.—Inhalation of phosgene, dichlorethyl sulfide, and especially of chlorine may be followed by chronic respiratory lesions. However, even heavily gassed dogs are essentially normal after two to twelve months; only a small minority show unimportant focal fibrosis (Koontz, 1925). Similarly favorable results are reported for soldiers. Four months after miscellaneous "gassing," the physical findings were normal in about 50 per cent of the patients; chronic bronchitis was present in 30 per cent, emphysema in 2 per cent (Berghoff, 1920). Exceptional cases develop persistent gastro-intestinal or nervous changes, due to hemorrhages into these situations.

The treatment of poisoning by pulmonary irritants may be directed against the immediate local irritation and bronchial spasm; the anoxemia and acidosis; the abnormal blood volume; the circulatory collapse; and the later bronchitis and secondary infections. Since these factors vary in importance and urgency at different stages of the intoxication, and in different patients, the treatment should also vary; but the pulmonary edema and the consequent asphyxia and circulatory collapse dominate all other indications.

In the following discussion the individual measures are arranged generally in the order of their application.

Protection is the first and most important measure. For military personnel this is secured mainly by appropriate masks and clothing. Civilians should speedily leave the gas area, walking against the wind or, if necessary, across the wind, and go upstairs, never into the basement.

If the *clothing* has been contaminated it should be removed, placed in a covered pail outdoors, and later washed with kerosene, then with water. If the *skin* has been wetted with liquid "gas", this should be blotted off, not rubbed, taking care that it does not touch the fingers. If the agent is "mustard gas", a chlorinated solution (household "bleach") should be applied. Hydrogen sulfide or "BAL" destroys lewisite. If the *eyes* have been exposed they should be rinsed thoroughly with sodium bicarbonate, a tablespoon of the powder to a quart of water. This may also be used for the nose if it feels irritated. A shower bath should be taken, with plenty of soap.

After exposure to asphyxiant gases, absolute rest is the important indication. Oxygen should be given to relieve cyanosis. Pain may be controlled with 10 to 15 mg. of morphine.

The usefulness of venesection and intravenous fluid is now doubted.

More or less asphyxia is always present. Every exertion, even standing, means a more rapid exhaustion of the difficultly obtainable oxygen; a more rapid accumulation of the difficulty excretable CO_2; and an added mechanical and chemical strain on the overloaded heart, which may easily bring on acute decompensation. The rest must be as absolute as circumstances permit. Sleep generally brings improvement. Restless and excited cases must have morphine. The indication of rest must be observed as long as the patient reacts to exertion by cyanosis, dyspnea or extra rapid pulse. Usually, if the rest is thorough in the start, the patient can return to light duties in a few weeks.

Warmth is a useful precaution against collapse. Severe cases should therefore be heated. Ordinary cases should at least be protected against chill, but should at the same time receive the benefit of fresh air.

Morphine is used as a sedative, to secure rest and to check spasmodic cough and mechanical trauma. It should be employed only when these indications exist and should be avoided when there is deep cyanosis. However, if the patient is very restless, he may receive morphine even though he be deeply cyanosed. The objection to morphine lies in the fear that it would depress the respiration at a time when the maximum respiratory ventilation is needed to offset the diminished lung area. This is largely obviated by employing rather small doses, not to exceed 0.015 to 0.02 Gm. The characteristic effect of therapeutic doses consists in a slowing but deepening of the respiration. This would counteract the rapid and shallow respiration that follows as a vicious circle on oxygen deficiency (Haldane and Meakins, 1918).

Ammonia inhalation, a few whiffs at intervals, during the first day, acts as respiratory stimulant, usually making breathing less exhausting. A few patients are made more uncomfortable by it, and in these it is not continued. Some early attempts were made to neutralize the inhaled chlorine by the continuous inhalation of ammonia. They were entirely unsuccessful, since the ammonia could only reach the chlorine excess in the upper air passages. These would not require the neutralizant, since they are quickly flushed by fresh air. The irritant action of the ammonia, if unskillfully used, may add to that of the chlorine so as to increase the local injury.

Analeptics: Brandy (small sips) is rather useful, until collapse becomes established. *Camphor* and *ether* have been used hypodermically, against the later collapse, with the usual discordant opinions as to their efficiency. *Pituitary solutions*, 0.5 cc. every three hours, intramuscularly, and *strychnine* are useless.

Atropine was proposed originally with the object of diminishing "pulmonary secretion." It proved entirely useless, since the exudate of pulmonary edema is of inflammatory origin and is not affected by atropine. It might be of advantage against *bronchial spasm* (Symes, 1915; Cow, 1915), but this is not a serious feature of gassing; and besides, the ordinary doses of atropine are apparently not sufficient to relieve it. In animals gassed with chlorine, Barbour, 1919, found the fatality unchanged by atropine.

Epinephrine was tried especially to relax bronchial spasm. It is efficient, although the relief is only temporary (1 cc. of 1:1000, hypodermically). It is not employed extensively, probably because the bronchial spasm is not an important factor in gassing. Barbour, 1919, found it inefficient in animals.]

Oxygen Inhalation.—The dominant indication, with the onset of edema, is to facilitate the access of oxygen, and later the elimination of carbon dioxide. The control of the carbon dioxide is difficult; but the anoxemia can be relieved considerably by efficient oxygen inhalation. This diminishes the cyanosis and increases the chances of survival. By its persistent use, patients may recover after being cyanosed and unconscious for two days.

Venesection was introduced early in the gas war, and maintained itself for all forms of irritant gases. Neither the clinical nor the experimental data are quite conclusive as to its efficiency for saving life, but the balance of the evidence is in its favor. The clinical relief is often striking, especially in the early severe cases, with deep-blue cyanosis and full pulse corresponding to acute asphyxial dilatation of the heart. The relief, however, may be only temporary. Bleeding must *not* be used when collapse has started, as indicated by a poor pulse; or when the condition of the patient is in any way immediately dangerous. This confines the usefulness of bleeding to the pre-edemic stage.

Saline Infusion.—During the stage of pulmonary edema, the blood becomes markedly concentrated, more viscid, and diminished in volume. Injection of normal saline (1 per cent of the body weight; *i.e.*, equal to the quantity of blood withdrawn at the venesection) has been tried to relieve this condition, but with doubtful benefit. Simple saline remains in the circulation at most half an hour and generally less, so that the benefit would at best be temporary; and the use of hypertonic salt or glucose solutions was found rather to increase the fatality.

Alkaline Treatment.—The most hopeless element in the treatment of the severe cases is acidosis, due to the inability of the edematous lung to eliminate carbon dioxide. Some good may be accomplished by introducing alkali into the blood; but the efficiency of this is limited when carbonic acid is not being excreted. This is an essential difference from other forms of acidosis.

Digitalis and ouabain were tried against the cardiac dilatation, but Barbour, 1919, found them useless with chlorine gassing. *Acetphenetidin and acetyl-salicylic acid* were tried against the headache, but are not advised, for fear of aiding the tendency to collapse.

Discharge of the Exudate from the Lungs.—Attempts to remove the exudate from the air passages mechanically are not promising. Coughing is a natural device for this purpose, but tends to become so violent as to threaten mechanical injury to the lung, and therefore generally rather needs to be allayed. Something can be accomplished by *position*. The head is turned to the side, and the foot of the bed raised 2 or 3 feet or higher, for a few minutes at a time. *Schaefer's method of artificial respiration* has been applied. It is not likely to do good, and may do harm. *Emetics* were used with the hope that the movements of vomiting would also expel some of the contents of the lungs. They appear to be ineffective for this purpose; and in the later stages the depression is certainly detrimental.

Expectorants.—On the first day ordinary expectorants are useless, and may indeed be harmful by exaggerating the tendency to nausea. An exception may be made for demulcents. *On the second day,* if the general condition is good, treatment of the bronchitis may be begun, with ammonium carbonate, 0.3 Gm., or ipeac tincture, 0.5 cc. every six hours. *Later,* the treatment of the bronchitis should be continued by the ordinary methods. Steam inhalation charged with Eucalyptus oil or Comp. Tr. Benzoin is used extensively.

Protection against poison gases is provided by masks covering the eyes, nose and mouth, and communicating with the air through layers of adsorbent and neutralizing chemicals. Those used in warfare (charcoal, permanganate and soda lime) are intended to protect at once against all the gases so far used, in their ordinary concentrations. This is a great advantage under field conditions. *The British type* contained essentially active charcoal and alkaline permanganate. *The German type* contained three layers: the inside layer, pumice with methenamine, which protects against phosgene; the middle layer, active charcoal; the outer layer, a mixture of baked earth, potassium carbonate and fine charcoal.

When only one gas need be considered, as under industrial conditions, more specialized absorbents may be preferred. *Chlorine* is so highly reactive that it can be easily neutralized. Even water is fairly effective. Thiosulfate and alkalis are the special absorbents. Soda lime is used against all *acid vapors;* cupric sulfate and activated charcoal against *ammonia;* charcoal against *organic vapors* (aniline, gasoline); catalytic metallic oxides against *carbon monoxide;* filter pads against *smokes* (Henderson and Haggard). *The detection and identification* of war gases are described in the Chemical Warfare Bulletin, 1940, *26:* 86.

Chronic poisoning by irritant gases has industrial importance, in view of their escape from chemical factories, etc. Even a small proportion tends to produce bronchitis and to diminish the resistance to infections (Ronzani, 1908: low concentrations of Cl, SO_2, NO_2). They may possibly cause cachectic conditions; but it is difficult to assign the limits between which these poisons are harmless, objectionable and dangerous.

CHLORINE GAS

The effects of inhaling toxic concentrations of chlorine gas were described in the general discussion of pulmonary irritants (see above).

Use in "Gas Clouds."—Chlorine was the first gas used in the war, being the sole constituent of the "gas-cloud" attacks of Ypres in April of 1915. It was effective, but because of the ease of protecting against it, was replaced almost entirely by phosgene mixtures, which were used almost exclusively in the gas clouds of 1916. *The concentration in cloud attacks* probably never rises above 1:1000, and more commonly is nearer 1:10,000. These are effective concentrations. With concentrations below 1:100,000, chlorine gas is practically ineffective under military conditions, although long exposure is followed by bronchitis.

Minor toxic effects of chlorine arise mainly in industry. Air contaminated with chlorine produces irritation of the conjunctiva and respiratory mucous membranes; 0.001 to 0.002 per thousand of air (volume) is harmless, although even 0.001 produces slight conjunctival irritation (Buergi in Heffter's Handbuch, 3, 1*:* 888); 0.003 is disagreeable, and 0.004 irrespirable (Matt, 1889). The foliage of plants is destroyed by concentrations which are not noticeable for man. The odor is recognizable in dilutions of one per million of air.

Habitual exposure to chlorine causes rhinitis with anosmia, conjunctivitis, bronchitis and stomatitis; anorexia, chronic gastritis, loss of weight, anemia, cachexia; insomnia. "Chlorine acne" is not due to chlorine as such, but to products of its action on tar lining of electrolytic tanks.

The mechanism of action of chlorine probably involves abstraction of hydrogen with liberation of nascent oxygen; and formation of hydrochloric acid. Chlorine is nearly twenty times more toxic than HCl gas, partly because of its relatively low solubility so that the action extends further down the respiratory tract.

Fate of the Inhaled Chlorine.—Chlorine is not absorbed as such. The chloride content of the plasma increases for a few hours after gassing, and the chloride excretion by the urine is raised on the second day following severe gassing. Presumably, chlorine-protein compounds are formed in the lungs and are absorbed, especially by the corroded tissue. These would break down in the tissues, liberating chloride ions, which would then appear in the urine.

Chlorine against Colds.—The inhalation of diluted chloride has been suggested as a treatment of acute respiratory affections. Vedder and Sawyer state that the concentration must be exactly 0.013 to 0.015 mg. per liter for an hour. The clinical results do not appear convincing. The chlorine can not exert any antiseptic actions under these conditions; and while it is conceivable that the irritation may sometimes produce a beneficial degree of hypermia, it is more probable that it would lower the resistance of the tissues.

Iodine and bromine are also local irritants, corrosives and antiseptics, but it seems more convenient to consider iodine with the iodides (see Index). Freshly made aqueous *bromine solution,* 1:1000 to 2000, applied on compresses to odorous wounds and fistulas, destroys the odor and produces little or no irritation (W. W. Babcock, 1945).

CHLORINE ANTISEPTICS

Strong and prompt germicidal effects are produced by chlorine as gas or in solution, and by substances capable of yielding "active" chlorine, such as the hypochlorites and chloramines (*i. e.,* compounds containing NCl groups). Toxins are also destroyed. Active chlorine compounds attack all organic matter, and are thus likely to be corrosive and to become inactive. These objections can be largely overcome by proper technic and selection of the preparations. *Inhalation of chlor-*

amine T or halazone dust in industries may sensitize to the production of asthma and rhinitis (S. M. Feinberg and Watrous, 1945).

Mechanism of Action.—Chlorine itself acts partly by oxidation, partly by chlorination of the organic matter. With the hypochlorites the chlorination appears to be the chief element. It is supposed to occur in the amino acid groups of the proteins, yielding chloramines. In chloramine-sulfonetoluene derivatives, the chlorine of the chloramine is still "active;" for instance, it liberates iodine from iodides. It is readily transferred to proteins, so that it acts essentially like hypochlorite, and is at least equally germicidal. The germicidal potency of sodium hypochlorite is about equal to that of free chlorine; the *hypobromite* has only about a hundredth of the activity of bromine, and *hypoiodites* react feebly with proteins and amino acids (Dakin, 1916).

Hypochlorites are available as *Chlorinated Lime* (*Calx Chlorinata, "Bleaching Powder,"* popularly misnamed *"Chloride of Lime"*), which consists mainly of a mixture or weak compound of calcium hypochlorite and calcium chloride, yielding 30 per cent of available chlorine. It occurs as a grayish-white granular powder of chlorine odor, partially soluble in water. It is an effective and cheap disinfectant, used largely as a disinfectant for excreta, but too irritant for application to the tissues. High dilutions are employed to sterilize water, especially for temporary emergencies. When swallowed, bleaching powder produces gastro-intestinal irritation. The treatment would be by evacuation and demulcents.

Disinfection of Excreta.—Six ounces of chlorinated lime are mixed with a gallon of water; a quart of this is added to each discharge and allowed to stand an hour.

Sterilization of Water.—Five to 15 pounds of chlorinated lime are used per million gallons according to the impurities and other conditions. This imparts a slight taste, but no other bad effects have been demonstrated. On a small scale a level teaspoonful is rubbed with 4 cups of water, and a teaspoon of this solution is added to 2 gallons of the drinking water, and left for at least ten minutes.

For Disinfection of the Hands.—These are moistened and rubbed with a little dry chlorinated lime and washing soda. If the powder or paste is left on the skin it causes burning, then rubefaction or mild dermatitis (Lebduska *et al.*, 1939). *Fetid wounds and ulcers* may be deodorized by washing twice daily with a solution of two tablespoonfuls in a basin of warm water (Muench, 1915). *For snake bites,* 10 cc. of a 1 per cent solution is injected hypodermically about the wound (Calmette, 1907).

Hypochlorite footbaths have been proposed for prophylaxis against *fungus infections,* but are useless, as it would require hours to kill the organisms (L. Schwartz, 1947).

Sodium Hypochlorite Solution, U.S.P. ("Labarraque's Solution"), contains about 5 per cent of NaOCl. *This solution is not suitable for application to wounds,* as it is too strongly alkaline; but when diluted with ten or twenty parts of water, it may be used as deodorant on ulcers; *Javelle Water* is a similar preparation of chlorinated potash.

Surgical Solutions of Hypochlorites (Dakin-Carrel Solution).—Continuous saturation of wounds with dilute, buffered hypochlorite solutions practically abolishes sepsis, dissolves dead tissue and promotes healing. The skin must be protected by petrolatum gauze, since it is often irritated even by the correct solution.

The solution is merely a tool in a specially developed surgical technic (Carrel and Dehelly, 1918), and its success depends on the care with which the principles of the technic are followed. To be effective, the solutions must contain between 0.43 and 0.48 per cent of available chlorine. Higher percentages are too irritant. The alkalinity must be adjusted to *p*H 9–10, for the tissues are more irritated on either side of this range (Cullen and Austin, 1918; Cullen and Taylor, 1918). The preparation and titration of the solution are fairly simple. It must be protected from light and kept not longer than a week. More permanent solutions can be prepared by electrolysis and the addition of a trace of permanganate or sodium silicate.

Solvent Action.—Hypochlorite solution is markedly solvent for necrotic tissues, even when the reaction is strictly neutral (Taylor and Austin, 1917). This helps to give better access to the bacteria. At best, however, the action is superficial, and damaged tissues must be promptly excised. Chloramine and Dichloramine T are without solvent action (Taylor and Austin, 1917). There is also a fibrinsolvent action on *living tissue cultures* (Lambert, 1916). The injury, however, to the phagocytes and other living cells is distinctly less serious than with most antiseptics. Silk *ligatures* are soluble in hypochlorite, and can therefore not be used with it. Catgut ligatures tend to slip, and thus incline to secondary hemorrhage (K. Taylor, 1917).

Intraperitoneal injection into dogs produces marked irritation, corrosion, collapse and death, or pericardial effusions and adhesions (C. S. Beck, 1929). *Intravenous injection* is relatively less toxic, but larger doses cause laking and delay the coagulation time (Mann and Crumley, 1918). The hypochlorite is rapidly destroyed by the blood serum, which partly accounts for the low toxicity (Dakin, 1916). *Blood Coagulation.*—The addition of Dakin's solution to blood (1:10) prevents clotting by interfering with the thrombin. Clotting occurs if tissue extract is added, so that the interference would not be important in wounds (Githens and Meltzer, 1918).

Dilution Solution of Sodium Hypochlorite, N.F. (Surgical Solution of Chlorinated Soda; Modified Dakin's Solution), is prepared by the dilution of the solution of Sodium Hypochlorite and addition of Sodium Bicarbonate, or by the interaction of sodium carbonate and assayed for chlorinated lime. It must not be confused with the stronger solution of Sodium Hypochlorite.

Chloramine T, *sodium para-toluene sulfonchloramide* (also called *chlorazene*), may be used in place of Dakin's solution and has the advantage that its watery solutions are practically stable. In equimolecular solution it is somewhat more germicidal than NaClO. This may perhaps be explained by less side reactions with nonbacterial proteins. Weight for weight, the germicidal power is somewhat weaker. It is less irritating and has but little solvent action on necrosed tissue. It is decomposed by oils.

It is employed in wounds as 1 to 2 per cent solution by the saturation technic. Strengths of solutions for eye, 0.1 per cent; nose and throat, 0.2 per cent; bladder and urethra, 0.25 per cent (Dakin, 1916; Eicher, 1917).

Chloramine T, U.S.P. (Sodium Paratoluenesulfonchloramide), contains about 12 per cent of active chlorine. White or faintly yellow crystals or crystalline powder having a slight chlorine odor; slowly decomposes on exposure to air, losing chlorine. Sol. in water (1:7) with alkaline reaction. Insol. in benzene, chloroform and ether. Decomposed by alcohol.

Dichloramine T, *toluene parasulfondichloramide*, is much more germicidal than chloramine T, but only traces dissolve in water. It is readily soluble in most organic solvents and oils, sparingly in paraffin and petrolatum. When such solutions are applied to the tissues, they give up the drug slowly and exert a continuous antiseptic action, until all the dichloramine T has been used up. A single application lasts for hours, or even a day, according to the strength of the solution (Dakin, Estell, 1917). There is little irritation of the skin. Catgut is not affected, so that the danger of secondary hemorrhage is avoided (Lee and Furness, 1918). The solution causes rather painful though short smarting of sensitive wounds; is more or less irritant to granulations and is said to retard epithelization; the dressings adhere to the wound, causing mechanical injury (Morrison *et al.*, 1918). The solvent action on dead tissue is less marked than with Dakin's solution (Taylor and Austin, 1917). Application to the peritoneum produces inflammation (Reismann and Magoun, 1918). Injection into the gallbladder is followed by induration. Introduction into the pleura is followed by rapid death (reflex?) (Grey, 1918). Dichloramine T is generally applied as solution in chlorinated paraffin. These solutions deteriorate rather rapidly, but retain considerable activity for a week or longer. The usual concentrations are: for *open wounds*, 2 to 10 per cent; sterilization of the *nasopharynx*, 2 per cent spray for fifteen minutes, several times daily (Dakin and Dunham, 1917); for *eye infections*, 0.5 to 1 per cent every four hours (Green and Green, 1918). Contact with yellow petrolatum destroys dichloramine T rapidly.

Chlorinated Paraffin, N.F. (*Chlorosane*), is a liquid paraffin treated with chlorine; used as a solvent for Dichloramine. A light yellow, clear, thick oily liquid; odorless; stable in air. Its chlorine is not "active" or antiseptic, but serves merely to protect the dichloramine.

Halazone, para-sulfondichloraminobenzoic acid, N.N.R., was introduced by Dakin and Dunham, 1917, for the extemporaneous purification of drinking water (one or two tablets of 4 mg. per liter). It sterilizes in about thirty minutes, and has little taste.

Succinchlorimide, N.N.R., (N-chlorosuccinimide,) yielding about twenty-six parts of active chlorine, is used for rapid disinfection of drinking water: 11.6 mg. per liter of water is reported to be effective in twenty minutes.

Chloroazodin, U.S.P., *azochloramid*, dichloroazodicarbonamide, yields about 38 per cent of active chlorine. It has the actions of chloramine and hypochlorite, but reacts less with organic matter and therefore has greater stability and higher bactericidal power in the presence of organic material. It is but little soluble in water, but an aqueous solution of 1:3500 to 1:1500, or an oil solution of 1:2000, may be used on infected wounds. *Solution of Chloroazodin*, U.S.P., a 2.6 per cent solution in glyceryl triacetate ("triacetin") deserves preference. It is more stable and can be diluted with three to eight volumes of water or with four of oil, for application to mucous membranes, or used undiluted on cuts, bruises and on dressings.

Dermatitis from "cutting oils."—Mechanics exposed to these oils tend to develop acne, folliculitis, comedones and keratoses, attributable to chlorine and sulfur compounds present in these preparations (Schamberg, 1920; S. M. Peck, 1944).

Chloracne.—Dermal cysts appear in nearly all electrical workers who are sufficiently exposed to electric insulating compounds. These dielectrics generally contain chlorodiphenyloxides, chloronaphthalenes, chlorodiphenyls, chlorophenols and chlorobenzenes; but the lesions are said to be purely mechanical, by obstruction of the pores by these agents, resulting in local keratinization (S. M. Peck, 1944).

PHOSGENE; CARBONYL CHLORIDE; $COCl_2$

Phosgene in itself is fairly indifferent; but in the presence of moisture it decomposes with the production of hydrochloric acid: $COCl_2 + H_2O = CO_2 + 2HCl$. Its effects are therefore relatively slight in the upper air passages, where the moisture is relatively small, and reach their maximum in the alveoli, where the air is saturated with water. With prolonged inhalation, however, enough is decomposed in the bronchi and trachea to produce corrosion. The site of action, as determined by the decomposition, explains the greater toxicity of phosgene as compared with chlorine. The slight degree of irritation of the sensory nerves in the upper air passages does not warn sufficiently against inhalation of the gas, so that the patient is likely to inhale it more deeply than he would equivalent concentrations of chlorine or other directly irritant vapors. Moreover, the reactive chlorine would be partly neutralized and bound in the upper air passages, while the indifferent phosgene would escape this destruction.

History and Use.—Before the first World War, this substance was known in toxicology mainly as the irritant product of the combustion of chloroform and carbon tetrachloride (which is used in fire extinguishers). Its use in gas clouds followed soon after that of chlorine. It incapacitates more slowly than chlorine, but is more dangerous in the end. For physical reasons, it was generally mixed with some chlorine when used as clouds. It was also employed extensively in shells.

Properties.—Phosgene liquefies at 8.2° C. The gas is about three times heavier than air.

Limits of Toleration.—The highest concentrations that can be breathed without prompt distress are 1:50,000 to 1:500,000; generally about 1:125,000. Even this, however, produces definite eye irritation. Gas clouds generally contain about 1:10,000. The high mortality may be judged by the result of animal experiments: of dogs exposed for half an hour to concentrations of 1:17,000 to 13,000, about 42 per cent died within two days; with concentrations 1:13,000 to 1:10,000, the deaths were 62 to 69 per cent. The concentrations for cats are reported by W. Wirth, 1936.

Differences in Symptoms from Chlorine.—The eye irritation is stronger than with chlorine. The sensory irritation of the respiratory passages is much less than with chlorine; for the irritation begins in the finer bronchial division, beyond the sensory nerves. Consequently there are generally no acute symptoms or cough. If cough occurs, it is less violent than with chlorine, so that there is much less emphysema. Although cyanosis and asphyxia may develop promptly, the ordinary onset is slow and insidious. The soldiers usually felt little inconvenience for an hour or two except some weakness; and then developed progressive pulmonary edema, with "grayish-white" collapse, that may soon terminate in death. Phosgene gas is much more likely to be followed by circulatory collapse; *i. e.*, it is much more likely than chlorine to develop irrecoverable pulmonary edema.

Superpalite, diphosgene, trichloromethyl-chloroformate (Cl COOC Cl_3), was the chief constituent of the "Green cross" shells, where it was usually mixed with some chloropicrin ("vomiting gas") or diphenyl chlorarsine ("sneezing gas"). It was perhaps the principal "killing" gas for shells, and is highly effective, acting essentially like phosgene, *i.e.*, by the liberation of hydrochloric acid on contact with water. The pathology and treatment are identical with those of phosgene. It is an oily liquid, of disagreeable, suffocating odor.

Palite, chloromethyl-chloroformate (Cl $COOCH_2$ Cl), is a liquid which was also used extensively in shells. It belongs to the same class as superpalite and phosgene.

NITRIC VAPORS

These constitute the brown vapors produced by the partial reduction of nitric acid or nitrates; when nitric acid acts on metals, as in etching, or on organic materials, as in the nitration processes of chemical industry, especially in the manufacture of nitrocellulose and picric acid; or by the accidental spilling of nitric acid on organic material, such as sawdust; or by the combustion of organic materials containing nitrates, in the combustion (not in the explosion) of nitroglycerin and of nitrocelluslose; the latter as "gun cotton," or "smokeless powder" in ammunition, or as "pyroxylin," the chief component of "celluloid," and of the highly inflammable nitrocellulose "films" used in photograph, cinema and radiography. The fatal catastrophes resulting from these combustions have led to the substitution of cellulose-acetate films, which do not form nitric vapors, and which have only a fire hazard, little greater than that of the combustion of paper. Many celluloid articles are still made of nitrocellulose, but they are not usually stored in large quantities in dangerous situations. Nitric vapor poisoning is quite common in the industries (review, von Oettingen, 1941).

Composition.—Nitric vapors consist chiefly of nitrogen dioxide, NO, and nitrogen tetroxide or peroxide, NO_2 (colorless) and N_2O_4 (dark brown). The last two, which are the more important, change readily into each other so that the end effects are virtually identical. The ratio of the peroxide increases with the temperature. The amounts produced from gun cotton, celluloid and photographic film vary with conditions. The smoke from these also contains carbon monoxide, cyanogen compounds and toxic tars (Proc. U.S.A. Chem. Warfare Service, 1929).

The effects consist in immediate irritation and delayed progressive inflammation of the exposed mucous membranes, especially of the respiratory organs. During exposure, there is some irritation of the eyes and the respiratory mucosae; but this subsides promptly when the exposure ceases, and the patient may feel practically normal for four to eight hours, but during this time fluid is accumulating in the pulmonary alveoli. When the edema has reached a sufficient degree, and especially when some slight exertion calls for extra oxygen, asphyxia sets in, with dyspnea, cyanosis, cardiac dilation and collapse. Death occurs in most cases in eight to forty-eight hours. The amount of pulmonary fluid is often profuse, and the blood becomes correspondingly concentrated and viscous; the hemoglobin is reduced, but there is no methemoglobin (E. Muntwyler *et al.*, 1929). If patients are not killed directly by the pulmonary edema, this often passes into secondary infective pneumonia, with death after several weeks; light cases may escape with laryngitis and bronchitis (Lehmann, 1913).

The *toxic concentrations* have been determined by K. B. Lehmann and Hasegawa, 1913. Some nitrite is formed after absorption, but the amounts and effects of this are insignificant in comparison with the irritant actions. *Film-combustion poisoning* involves also other gases. The acute deaths, which occur immediately or within a few minutes, are due to carbon monoxide, possibly with the admixture of cyanide, which is also formed. The later fatalities take the ordinary course of the nitric patients. The smoke also contains a toxic tar, which produces methemoglobin (Sollmann, Ray and Hambourger, 1931); but this does not appear to be concerned in the acute fume poisoning.

The treatment should consist in absolute rest for twenty-four to forty-eight hours after the exposure, to minimize the need of oxygen (Walton, 1925). Oxygen inhalation may be begun with the first sign of edema. Chemical antidotes (thiosulfate injection, etc.) are useless after the gas has been inhaled. The treatment of the developed edema is that of other acute pulmonary edema (glucose injection, etc.); but the prognosis is bad. Sedative doses of morphine may be administered without hesitation, to diminish anxiety and dyspnea. Larger doses may be dangerous. Emetics, atropine, epinephrine and pituitary injections are useless and possibly harmful. The mucous membranes may be treated with boric acid lotions and protected by demulcents.

Protection.—The fumes are freely soluble in water, and a damp cloth furnishes considerable protection. A sponge wetted with sodium carbonate or, better, sodium thiosulfate solution, or the army gas masks, are more effective. Industrial fumes should be removed by adequate ventilation. Film fires should be flushed with water; chemical extinguishers are useless.

Dimethyl sulfate $(CH_3)_2SO_4$, produces corrosion of the respiratory mucosae, probably by hydrolysis into sulfuric acid (Strothmann, 1929).

Sulfur dioxide is discussed under sulfur compounds (see Index).

Chloropicrin, "vomiting gas," *nitro-trichloro-methane, nitrochloroform* $(C\,Cl_3{\cdot}NO_2)$.—All irritants, even the asphyxiants, may provoke vomiting; but chloropicrin was used in the war particularly for this purpose. It is a neutral, colorless fluid, noninflammable, boiling at 113° C. It was therefore used in shells, but may be used in gas clouds if mixed with more volatile substances. It was intended partly to induce the men to remove their masks, and thus inhale the more toxic substances (diphosgene, diphenyl chlorarsine) with which it was generally mixed. It is itself a potent pulmonary irritant, however, intermediate between chlorine and phosgene. It is an effective insecticide fumigant (Chapman and Johnson, 1925).

Effects.—Chloropicrin irritates all surfaces. It therefore produces lacrimation, bronchitis and pulmonary edema, as well as vomiting. It also irritates the skin. Dilutions of 1:1,000,000 are detected by the *eyes* of most subjects. Concentrations of 1:200,000 would incapacitate victims within ten minutes. The eyes smart and pain, as with all lacrimators. There is considerable irritation of the *throat*, cough, etc. Exposure is generally followed by *bronchitis* and asthmatic attacks. Death may follow from the pulmonary complications. In experimental exposures of dogs to moderate concentrations the *blood picture* is that of phosgene poisoning, *i. e.*, a pre-edemic fall in hemoglobin, followed by a rise as edema develops. With high concentrations, the edema may set in so rapidly that the hemoglobin appears increased almost from the start. The *emetic effect* is presumably due to direct gastric irritation from swallowing saliva impregnated with the poison. Contact with the liquid causes severe *burns*, usually with blistering, and may lead to ulceration. Abrasions, if exposed to the vapors, tend to become septic. The *kidneys* appear to be injured more frequently than with any of the other "gases." For this reason prolonged exposure is dangerous even in low concentrations.

After-Effects.—Chloropicrin poisoning is likely to be followed by serious sequels: severe anemia, with general asthenia; weak and irregular heart, sometimes cardiac dilation; the patient ages rapidly. There is a liability to recurrent asthmatic attacks, leading to emphysema. (These are treated like ordinary asthma, by epinephrine, morphine and atropine.) Those who have been poisoned appear to be hypersensitive to the poison. This is also observed in animals.

Chloracetophenone, $C_6H_5.CO.CH_2Cl$, a white crystalline solid, produces irritation of the mucous membranes, the conjunctiva being especially susceptible. Very small quantities cause the eyes to water, smart and pain so as to put men out of action, without any permanent harm resulting from these concentrations. Higher concentrations irritate the nose, pharynx and skin. It is the principal "*tear gas*" or lacrimator used in grenades, for protection and in civil riots as well as in warfare.

Effective Concentrations.—Lacrimation begins with 0.3 to 0.5 mg. per cubic meter, nasal irritation with 1 mg.; 2 mg. makes seeing impossible; 4 to 5 mg. is the highest concentration that can be tolerated for one minute. The pain protects against exposure to higher concentrations which would otherwise cause pulmonary edema. Ordinarily, the symptoms go no further, and recede rapidly after exposure ceases. Within an hour or two the patient is practically normal, except for slight hyperemia of the eyes, which may last twelve hours. There are no toxic after-effects, and men are fit for duty as soon as the eye irritation lets up; but the conjunctival irritation is sometimes followed by secondary bacterial invasion. Direct contact with the cornea may produce permanent opacity.

Treatment.—Washing with sodium sulfite solution gives prompt relief; for the eyes, 0.4 Gm. in 25 cc. of water and 75 cc. of glycerin; for the skin, 4 per cent in 50 per cent alcohol. If sodium sulfite is not available, the surface should be washed with glycerin, 50 per cent alcohol or with whiskey (W. D. McNally, 1931). The substance is but little soluble in water. Its odor is similar to that of locust blossoms.

Other lacrimators are numerous, but generally less specific and more harmful. They include phenylcarbylamine chloride $(C_6H_5NCCl_2)$, used chiefly by the Germans in the first World War; benzyl and xylyl bromide, chloride and bromcyanide; bromated and chlorinated ketone and acetone; chlorosulfonates, bromacetic and iodacetic ether; acrolein; stannic chloride.

CHLORARSINES

Diphenylchlorarsine, $(C_6H_5)_2AsCl$ and diphenylaminechlorarsine, $(C_6H_5)_2NAsCl_2$ (*adamsite*) were used as "*irritant smokes*," chiefly to enforce the inconvenience of masking. They cause extreme distress, immediate or delayed for half an hour, likened to extreme seasickness, together with acute sinusitis and toothache! They irritate the eyes, nose and throat, with copious watery nasal discharge; characteristic severe pain beginning at the base of the nose and spreading through the sinuses, sneezing and coughing with pain in the chest; nausea and vomiting; marked mental depression and muscular weakness. Sensory disturbances, generally temporary, set in later, sometimes not till the third or fourth day (S. A. White, 1938).

Diphenylchlorarsine is used as a very fine powder. Diffused in the air in the proportion of 1:1,000,000, it produces intolerably violent sneezing for some fifteen minutes. Even more dilute mixtures are effective sneezing agents. *Higher concentrations* act as respiratory irritants. With animals, fatal concentrations produce inflammation of the whole respiratory tract; fibrinous bronchitis, pulmonary edema or pneumonia. The toxicity is as great as that of phosgene (Underhill, 1918). Intraperitoneal injections also produce pulmonary congestion. There is a conspicuous absence of the intestinal and renal changes produced by ordinary arsenicals.

Treatment.—Inhalation of chlorine was reported to relieve the symptoms by forming nonirritant compounds with these arsines (Walton and Eldridge, 1929).

Chlorvinyldichlorarsine, $ClCH{:}CH.AsCl_2$, "*Lewisite,*" a liquid with rose-geranium odor, which penetrates through rubber, acts as a vesicant, somewhat like "mustard gas," but with quicker absorption and with some systemic arsenical actions, especially on the kidneys. Severe illness results if 0.3 cc. is left on the skin; 1.4 cc. may produce death in three hours to five days. Its effects on the skin were studied by Rovida, 1929. It produces large blisters, but not surrounded by erythema. It may penetrate to the bone. The blisters should be evacuated (in contrast to mustard gas burns) to diminish the systemic arsenic effects. Sorbitol-gelatin film furnishes some protection (C. J. Carr, 1943). Eye burns under field conditions produce superficial irritation of the cornea, usually without permanent damage (D. G. Cogan, 1943). They may be treated with prompt application of hydrogen peroxide solution diluted with three parts of water, but the most effective antidote against all arsenial agents is 2-3 dithiolpropanol "BAL," Dimercaprol (British Anti-Lewisite) (see Index).

Ethyldichlorarsine acts similarly to lewisite, but is milder. It was proposed as a "sneezing gas."

DICHLORDIETHYLSULFIDE
(DICHLORETHYLSULFIDE)
"MUSTARD GAS"
CHLOROETHYLAMINES
"NITROGEN MUSTARDS"

Dichlorethylsulfide $(C_2H_4Cl)_2S$, acquired great importance as the "*blistering gas*" of gas warfare. It was also known as "*Yperite,*" "yellow cross shells" and thiodiglycol chloride. It is an oily fluid of sharp odor, but not chemically related to "mustard oil" It differs from the older war "gases" in that its serious effects are not confined to the respiratory tract. Pulmonary lesions, when they occur, are indeed the most fatal manifestations; but there are important actions on the eyes and skin, and sometimes fairly severe gastric disturbances. Direct systemic effects are only faintly indicated in field or factory intoxications.

It penetrates deeply, injures the blood vessels and blocks the circulation, resulting in severe inflammation and tissue necrosis. Contact with the fluid or its vapor does not produce any immediate effect whatever; but after a latent period of some hours, intense inflammation develops at the site of contact, even with minute traces. This leads to vesication, followed by local necrosis with slow healing. The lesions are superficial and extend but little beyond the actual contact. It produces marked leukopenia, with involution of the lymph nodes and aplasia of the bone marrow (O. Bodansky, 1945). Secondary infections are common, as the resistance is lowered. The intoxication is usually strictly local, involving the skin, the eyes, the respiratory and sometimes the alimentary mucosae, according to the method of application. Systemic intoxication usually occurs only by intravenous injection. The treatment of the local lesions is mainly by cleanliness and emollients, similar to that of burns. Oils protect the skin only slightly. If the patient is seen immediately after exposure, the poison may be partly removed by scrubbing with kerosene; but the penetration is so rapid that this treatment is not successful if delayed for fifteen or thirty minutes.

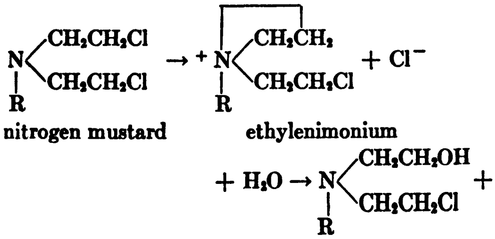
Nitrogen mustards are analogous compounds of nitrogen, chloroethyls (C_2H_4Cl) taking two (bis) or three (tris), more commonly two (bis), valences of nitrogen. The third valence of the bis compounds is taken by an alkyl group; this furnishes a large series of compounds differing in degree of reactivity and therefore capable of biologic adaptations. Nitrogen mustards are also casualty-producing vesicants, but their chief interest lies in their systemic actions, especially their toxicity to lymphoid tissue, suggesting possibilities in the treatment of leukemic conditions. The effects on cells resemble those of x-ray irradiation. Dichlordiethylsulfide produces the same actions, but the amines are more adaptable (reviews, A. Gilman, 1946; Gilman and Philips, 1946). At present, the therapeutic usefulness of nitrogen mustards appears to be limited to widely disseminated, rapidly growing neoplasm, but the improvement is only temporary (C. P. Rhoads, 1946).

Chemical Properties.—The toxic action of dichlorethylsulfide is intimately connected with its constitution, particularly with the presence of the two chlorine atoms. If these are either diminished or increased, the activity is destroyed. This may be accomplished, and the "mustard gas" may be "killed" by hydrolysis, chlorination and by reducing agents evolving nascent hydrogen; less efficiently by oxidizing substances.

Hydrolysis.—Dichlorethylsulfide is hydrolyzed by water, probably mainly according to the equation: $S(C_2H_4Cl)_2 + 2H_2O = S(C_2H_4OH)_2 + 2HCl$. The hydrolysis starts promptly and proceeds fairly rapidly for the dissolved substance, but proceeds slowly for the undissolved excess.

Hydrolysis Theory of Toxic Action.—It has been suggested that the dichlorethylsulfide penetrates as such into the cells, where it is slowly hydrolyzed, resulting in a liberation of free acid within the cells; and that in this free acid is the toxic agent (Lynch, Smith and Marshall, 1918). It is established that the substance is hydrolyzed before it is excreted; and there is proof that this hydrolysis may occur within the cells at the place of application, at least in starfish ova (Lillie, Clewes *et al.*, 1918, 1919). The proof, however, is not conclusive. Related substances, such as dichlordiethylsulfone, which practically do not produce acid, are nevertheless vesicant; while dichlordimethylsulfide, which produces acid more readily than the "mustard gas," is not vesicant (Flury and Wieland, 1921; Peters and Walker, 1923).

Current Theories of Mechanism.—Gilman and Philips, 1946, attribute the toxic effects, local and systemic, to the formation of highly reactive *cyclic onium* cation, ethylene sulfonium or ethylene imoniums. These act on the carboxyl, amino and perhaps other groups in proteins and are thereby cytotoxic, apparently through inactivation of essential cellular enzymes, especially phosphokinases, concerned with the transfer of PO_4 to and from adenylic compounds. The sequence of reaction of the nitrogen mustards may be represented as:



$$\underset{\substack{|\\R}}{N}\left\langle\begin{matrix}CH_2CH_2Cl\\CH_2CH_2Cl\end{matrix}\right. \rightarrow {}^{+}\underset{\substack{|\\R}}{N}\left\langle\begin{matrix}CH_2CH_2\\CH_2CH_2Cl\end{matrix}\right. + Cl^-$$

$$+ H_2O \rightarrow \underset{\substack{|\\R}}{N}\left\langle\begin{matrix}CH_2CH_2OH\\CH_2CH_2Cl\end{matrix}\right. + H^+.$$

Sulfur mustard depresses oxygen consumption, aerobic and anaerobic glycolysis and pyruvate oxidation in minced brain, mammalian skin, avian erthrocytes and other tissues, but this requires higher concentrations than exist in living animals. Most enzymes are resistant or only moderately sensitive.

The cytotoxic action appears analogous to irradiation in many ways. The *mitotic* activity of a wide variety of cells is susceptible to inhibition by minimal doses. Somewhat higher concentrations produce *nuclear fragmentation*. Threshhold doses act on *chromosomes* in Drosophila, resulting in inheritable abnormalities.

Systemic effects, obtainable most conveniently by intravenous injection of sublethal doses of nitrogen mustards, involve especially the *blood-forming organs*. The lymphoid tissue throughout the body is fragmented and atrophied; the bone marrow shows swelling of the cells, disappearance of mitotic activity, and aplasia. There is marked decrease of lymphocytes, granulocytes and thrombocytes, and moderate decrease of erythrocytes. These effects are in direct ratio to the dosage. The *gastrointestinal epithelium* is also markedly affected, with vacuolization, nuclear swelling, desquamation and hemorrhage.

Therapeutic applications of the high toxicity for lymphoid tissue are under trial, by intravenous injection of saline solutions of the crystalline hydrochlorides of the nitrogen mustards, especially methyl-bis (-chloroethyl) amine ("Dema"), 0.1 mg. per Kg., in courses of one to 7 daily injections. Experimentally, they lead to rapid dissolution of transplanted lymphosarcoma of mice, but the dose borders on the toxic and the tumors return. Hodgkin's disease responds with remission of the same kind and degree as with x-ray therapy, rapid alleviation of symptoms and of the lymphadenopathy. The administration must be repeated in one to eight months. The results are less favorable in lymphosarcoma, and disappointing in lymphogenous and myelogenous leukemias. The dosage must be limited to avoid hematopoietic damage. The margin of safety is small, but *untoward symptoms* are generally less severe than with irradiation. At present the superiority over this is questionable, but it is hoped that better results may be secured by more favorable derivatives (Gilman and Philips, 1946).

The systemic toxic symptoms begin in a few hours with nausea and vomiting. Diarrhea starts within a day and becomes severe. Vomitus and stools may show blood. Loss of fluid and electrolytes by these actions results in marked anhydremia, with decrease of intracellular water and potassium, ending in prostration and fatal shock. With smaller doses the changes set in later, the intestinal symptoms in one or two days, the leukopenia in three to six days. Survivors recover completely (Graef *et al.*, 1946; L. S. Goodman, Wintrobe *et al.*, 1946; L. O. Jacobson, Spurr *et al.*, 1946).

Acute effects are seen only with supralethal doses. Central nervous excitation leads to convulsions and acute death; the parasympathetic stimulation, to salivation and miosis, followed by parasympathetic paralysis. *Subconvulsive doses* of nitrogen mustards produce progressive muscular paralysis, finally including the respiratory muscles and producing death (Gilman and Philips, 1946).

Historical.—Dichlordiethylsulfide and its toxic effects were discovered by Victor Meyer in 1886 (Ber. deut. chem. Gesell., v. 19, p. 3259; v. 20, p. 1729). Its military use as a war gas was apparently first suggested by J S. Haldane in 1915, but the Allies turned it down as not being sufficiently fatal (J. B. S. Haldane, 1938). It was first used on a large scale by the Germans at Ypres, July 12 and 13, 1917, and scored heavily, since its peculiar properties were not at once appreciated. It differs from the other gases in two essential respects: (1) its effects are delayed several hours, so that effective protection is apt to be neglected; and (2) it is very persistent, so that areas that have been shelled with it are infective for several days. This persistence is due to the limited volatility of the liquid at ordinary temperatures. When atomized by the explosion of the shell, it spreads as a mist, which condenses as a liquid film on any solid substance, leaves, cannon, the ground, etc.; and thus forms deposits that are dangerous both by direct contact, and because their slow evaporation keeps up a prolonged saturation in the air with the poison. This holds especially for valleys, trenches, etc., where the air is stagnant. *Nitrogen mustards* were developed during the second World War, but were not used.

Other Skin Irritants.—Hanzlik *et al.*, 1919, give a survey of the results from a large number of substances.

Physical Properties.—Dichlordiethylsulfide is a colorless or pale yellow, heavy, oily liquid of neutral reaction. When pure, it has a faint but penetrating odor, reminiscent of stale ether. The odor of the crude product is more pronounced and similar to that of garlic. It is due mainly to contamination with ethyl sulfide. This is the source of its popular name, "Mustard Gas," for it is not derived from true mustard oil. Toxic concentrations of mustard gas can generally be smelled in the air. *Nitrogen mustards* are liquid, or solid of low melting point; odorless or of a slight fishy odor. They hydrolyze fairly rapidly, forming toxic products.

Solubility.—Dichlorethylsulfide is soluble in fats, fat solvents and alcohol, but is only slightly soluble in water. Its solubility increases with the temperature, but it is rapidly hydrolyzed.

The cause of the delayed action of dichlordiethylsulfide has been attributed to gradual hydrolysis. This could scarcely explain the delay of over a day. More likely it is merely the expression of the sluggish character of the inflammation.

Destruction of mustard gas may be accomplished by chlorination or dechlorination; or less efficiently by other chemical changes. Free chlorine, as gas or dissolved in carbon tetrachloride, introduces a third chlorine atom into the dichlorethylsulfide, forming "monochloro-mustard gas," which is nonirritating. Sulfur dichloride, pure or dissolved in carbon tetrachloride, is also highly effective, and is used to "kill" the gas. It is, however, corrosive to organic matter. BAL does *not* detoxicate the mustard.

The development of symptoms under field conditions without protection is usually in the following order: No effects are felt *immediately* on exposure, except in high concentrations, when there may be tendency to sneeze, with or without smarting of the eyes. Hemorrhage, especially from the nose, is a common early symptom (Berghoff, 1919). The first definite symptoms are generally from the eye, starting *two or three hours after exposure,* with smarting and watering, proceeding to reddening, pain, edema and all the phenomena of acute conjunctivitis. The nose also reacts early with increased secretion and sneezing. The throat likewise becomes sore. *In four to sixteen hours after exposure,* these symptoms have become much more marked and distressing. The eyes are discharging and very painful; the nasal discharge is more purulent; the voice is husky or suppressed. Nausea, retching and vomiting, associated with epigastric pains, occur in a large proportion of cases and may recur at frequent intervals for several hours. In severe cases, they may become intense and prolonged. Diarrhea may set in, but is rather exceptional. Skin rashes also show in this period, as a dusky erythema of the exposed parts of the body, and in the axilla, crotch and genitals. *At the end of twenty-four hours,* the eye symptoms have assumed a characteristic form in the severer cases. They are very painful, with the lids swollen almost shut, and oozing tears. There are photophobia and blepharospasm, and generally frontal headache. The exposed skin is further reddened and swollen and may be itching. The nose discharges freely. The throat feels raw and burning. Aphonia may be complete. A dry harsh cough may develop. The respiration is fairly normal. Death practically never occurs during the first day. *During the second day,* the skin erythema may have developed into blisters, sometimes of large size, with the scrotum and penis especially painfully swollen. (The future course of the skin lesions will be discussed later). The eyes become somewhat less painful, although the acute inflammation may persist for several days. This is also the time when the inflammation of the respiratory tract becomes conspicuous in severe cases. The expectoration becomes abundant, mucopurulent, sometimes with large sloughs of tracheal mucosa. This is complicated by secondary infection of the necrotic respiratory membranes. Fever sets in, with rapid pulse and respiration. The infection may terminate in bronchopneumonia, with death anywhere between the second day to the fourth week. Most cases are of a milder type; especially as troops acquire familiarity with the gas and apply the protective measures more stringently. In the opening of the 1918 campaign, the mustard mortality was slight. There were few actual blisters, although minor rashes were common. The conjunctivites were less severe; the laryngites fairly mild, but almost universal. Most mustard field cases have only slight respiratory catarrh. Only about 10 per cent are burns (Underhill, 1918). During the hot months, there is an increase of the pulmonary lesions, perhaps because of the greater volatilization.

The toxicity for animals is fairly uniform, with less variation for species than there is for individuals (Lynch, Smith and Marshall, 1918; Reed, 1918, 1920). Air saturated with dichlorethylsulfide at ordinary temperatures would hold about 0.5 mg. per liter. This would be fatal if breathed for seven minutes. Concentrations of 0.01 to 0.02 mg. per liter have a 50 per cent mortality with a two-hour exposure, and 60 per cent with four hours. Less than 0.01 mg. per liter (1:700,000 by volume) is not fatal even with eight hours' exposure, but produces slight symptoms from the mucosae (conjunctiva, nose), and loss of appetite.

Lesions in Upper Respiratory Tract.—The corrosive effects on the epithelium are identical with the corrosion of other epithelial surfaces. Their intensity diminishes from the mouth and nose toward the lungs. The bronchi are involved only in the severest cases. Subepithelial edema is much less than in the skin or conjunctiva. The primary action is followed by local catarrh or diphtheritic lesions from the nose to the bronchi, even in the mildest cases. In the more severe, there is a marked pseudomembrane formation, secondary purulent bronchitis and bronchopneumonia (Warthin and Weller, 1919). The rhinitis, laryngitis, tracheitis and bronchitis play a conspicuous part in the minor as well as in the severe intoxication of mustard gas. The *alveoli* are but little affected directly, presumably because most of the substance is bound and absorbed before it can reach them. Consequently there is no acute pulmonary edema, in the early stages, and no fluid or froth in the air tube; although there may be considerable congestion and some epithelial desquamation. The serious cases become infected by bacteria, and then change to an intensive bronchopneumonia, with its ordinary phenomena, which may bring about a secondary edema. In case of *recovery,* the ulcers of the mucosae heal slowly. Ulceration of the trachea may be followed by constriction of its lumen.

Eye Lesions from Mustard Gas.—The cornea and conjunctiva are highly sensitive to the "mustard" irritation, and present the earliest and often the most serious symptoms after unprotected exposure to the vapor. Identical effects are produced by contact with the liquid poison. A previous eye burn increases the susceptibility. Light cases may heal in two or three days. In severe poisoning the inflammation is intensely painful for several days, and ocular symptoms may persist for several weeks. The deeper structures of the eye are not affected, except under extreme conditions. Nearly all cases recover without permanent injury, except at most some reduction of vision from cicatrization of the cornea. Severe eye injuries resulted in only about 1½ per cent of the gassed (Tenlieres, 1918). The course and pathology of the lesions have been studied in detail on rabbits (Warthin and Weller, 1918). The effective concentrations for man are reported by Reed, 1920; for animals, by Marshall *et al.*, 1918.

Treatment of the Eye Lesions.—The conjunctiva should be kept clean by frequent irrigation with saturated boric acid, or with 1 per cent sodium bicarbonate, followed by a few drops of oil. Continuous mydriasis and exclusion of light are advised (S. A. White, 1938). Lightweight cold compresses of saturated boric solution should be applied continuously for twelve to twenty-four hours, or longer if needed, to relieve the pain and discomfort, reduce the congestion and protect the eyes against light. Pressure on the eyelids must be avoided. This treatment tends to prevent adhesion of the eyelids. If they do become glued together, they must be soaked in boric or bicarbonate solution until they can be opened without force.

If liquid "mustard" is splashed into the eyes, this should be washed at once with the 1 per cent dichloramine solution.

Skin burns differ from the course of ordinary toxic dermatites: in the length of the latent period and in the absence of pain until the ulceration stage has set in. Not only are mustard burns imperceptible when first received, but they remain painless until the blisters break, about the third or fourth day. This is not due to anesthesia. In the mild rashes, the skin edema causes intense itching about the same time.

The tedious and slow healing of the necrotic lesions is due to injury of their blood vessels. They generally become somewhat infected, but only superficially. There is little or no fever. The lymph nodes are swollen and painful quite early.

Dichlorethylsulfide penetrates the skin very rapidly. The effects of the liquid or vapor are identical, differing only in extent and intensity, vapor burns being usually more extensive but less severe. The susceptibility varies considerably in different individuals, and is also influenced by temporary conditions. The burns range in intensity from simple rubefaction, through edema, vesication and necrosis. Although severe, the inflammation remains confined to the skin, perhaps because the circulation prevents its accumulation in the deeper structures (Warthin and Weller, 1918; Marshall, Smith and Lynch, 1918; Sollmann, 1919.)

Course.—The inflammation has a rather striking course. There is a latent period of a half hour to two days, before any inflammation can be seen or felt. The inflammation gradually increases, then remains stationary, and slowly heals. The duration of these stages depends on the severity of the exposure. Light burns appear late and heal early; severe lesions appear early and heal late

Skin Rashes.—Erythema occurs as the first stage of all "mustard" lesions. Vapor burns and dilute solutions (*f. i.*, saturated watery solution) do not usually progress beyond this stage. Practically everyone who works with or around mustard gas is liable to the frequent occurrence of these rashes, which are probably the most common form of "burns" in the field. Rashes also commonly surround the blister burns for considerable distance, but the excess of the dichlorethylsulfide evaporates from the cloth, and the vapor spreads. The axilla and groins are especially affected. Severe grades may develop minute miliary blisters. These may give the skin the appearance and feel of pebbled oilcloth. The edema is confined to the epidermis and papillary layer. The inflammatory phenomena persist for several days, and then gradually subside, within a week or two, leaving generally some pigmentation, and hypersusceptibility to irritation.

Pigmentation may take various forms. It may have the red appearance of weather exposure, or be more or less "tanned" as by the sun. In severe burns, the pigmentation is sometimes almost black, but confined to the superficial desquamating epidermis.

Erythema Preliminary to Vesication.—Erythema also constitutes the first stage of the blister burns. In that case it appears much earlier, is more sharply localized, and undergoes vesication after one or two days.

Prognostic Significance.—The time when the erythema first becomes noticeable is of prognostic value: If the skin shows pink or livid spots within one and one-half hours after exposure, the burn will develop into a deep blister, and probably undergo ulceration and scarring. If the pink spots start between two and three hours after exposure, the blisters will be superficial and will probably heal without ulceration, and without real scarring. If the rash is delayed for twelve to forty-eight hours, it will not develop into blisters.

Blister Burns.—When strong vapor or especially when liquid dichlorethylsulfide comes in contact with the skin, the erythema passes into vesication. The first noticeable change is a silvery appearance of the skin, produced by loosening of the epidermis. This is then raised by the accumulation of fluid; the blister is usually well developed in twelve hours, and reaches its maximum size in about twenty-four hours. The blisters at first are very tense, often an inch or more high, and may be up to 3 or 4 inches in diameter. They are filled with a transparent gelatinous material, *i. e.*, practically coagulated plasma. If they are opened at this time, the contents stand up like a jelly, and require to be pushed or scooped away.

Between the second and third days the serum begins to separate from the clot. The "skin" of the blister becomes thin and wrinkles as the serum is absorbed, and opaque balls or shreds of the fibrin are seen within the blister. Generally the blister breaks, and the serum, as it separates, drips in a continuous slow stream from the wound. This gives the patient a distressing and uncomfortable appearance, especially if the genitalia are involved. In fact, however, the process is painless up to this time. If the blister is undisturbed, it may be a week before it is fully collapsed.

About three days after exposure, the blister begins to become painful, especially on exposure to air, on mechanical contact, or when treated with chemicals. This sensitiveness increases rapidly to the fifth or sixth day, and the pain becomes severe. This hypersensitiveness lasts for two or three weeks, or even longer if ulceration develops. However, the lesions become painless long before the ulcers are healed.

The size of the blisters is not an indication of the severity of the lesions: the largest blisters may be healed in two or three weeks, while another smaller blister, nearby, goes through a tedious ulceration that is healed only by scarring after six or eight weeks. The severest lesions (the gangrenous form) do not blister at all. The process apparently involves the corium more or less, although it does not often destroy the epithelium so deeply that it can not re-cover the wound. Statements that it "corrodes to the bone" have no foundation.

This condition of the wound remains practically stationary for two to four weeks. Then further necrosis ceases quite noticeably, about the same time that the hypersensitiveness diminishes. A pale pink ring of epithelium starts from the periphery to cover the wound, which meanwhile may form exuberant granulations. Toward the end of the fifth or sixth week, practically all wounds are essentially healed, with or without cicatrization. The new skin over the burned areas appears shiny and often pigmented, as in x-ray burns.

Burns of the genitalia differ somewhat from the type. When the scrotum is involved, the testicles become sensitive. The condition clears about the same time as the skin lesions. Blisters of the penis may come on quite slowly, and turn into tedious ulcers, which heal much more slowly than other lesions. Infection of the meatus may cause a urethral discharge.

The most severe burns (the gangrenous type) differ from the blister type from the start. Smarting and burning are felt within an hour after receiving the burn. The skin at that time is intensely blanched. By the next day, the burn proper is of a livid, cadaveric color. It does not vesicate, but forms a depression, surrounded by a continuous ring of blister. After a week or so it breaks down into an ulcer, and the entire thickness of the skin may be removed in a mass. The wound remains painful for three or four weeks. Healing occurs after five to seven weeks by cicatrization.

Systemic Reactions of Mustard Burns.—Dichlorethylsulfide applied to the skin does not reach the circulation in sufficient amount to produce systemic lesions; nor are the mustard burns, even when extensive and deep, accompanied by the acute toxic phenomena of fire burns. The temperature remains practically normal. Extensive burns may produce temporary collapse, mainly if not entirely of psychic origin. Later on, the pain is likely to interfere with sleep. The urine should be watched.

Secondary Furunculosis.—Mustard burns lower the resistance of the skin to infection. The blisters are usually followed by a crop of furuncles or pustules, generally on and around the burned area. Men who work with mustard commonly have this complaint even when they have had only superficial rashes.

Increased Susceptibility of the Skin.—Healed mustard burns are hypersusceptible to the poison, and also to mechanical injury. A light contusion may result in a blister. This hypersensitivity is confined to the burned areas and does not extend to the remainder of the skin.

Microscopic changes in mustard burns have been described in detail by Warthin and Weller. The epithelium shows hydropic and other degenerative and necrotic changes within two hours. The edema in the early stages is confined to the epidermis and papillary layer, and does not extend much more deeply. In severe burns, the vessels in the affected area are greatly damaged and collapsed. This results in local anemia in the earlier stages, with marked exudation and leukocyte migration.

Skin Lesions in Animals.—Blistering does not usually occur in the customary experimental animals, including monkeys. Otherwise the lesions are essentially the same as in man (Marshall and Williams, 1918). Horses are said to be about five times more sensitive to vesicants than is man. Ducks respond with large blisters to mustard gas and to lewisite (L. Goldman *et al.*, 1944).

Susceptibility to Skin Burns.—A visible reaction requires, in a "tolerant" individual, a concentration more than a hundred times greater than will produce results in a hypersensitive. Negroes are notably tolerant. The tolerance for a given person does not change greatly with time, if other conditions are uniform. It is also fairly alike for the skin of the entire body, with the exception of a few special regions. The axilla and crotch are hypersusceptible (largely because of their moisture), but the thick-skin palmar surface of the hand and fingers is relatively insusceptible. The area of a previous burn is hypersusceptible; but hypersusceptibility appears not to be especially frequent among those who have worked constantly with "mustard" and have received severe and extensive burns (Sollmann, 1919).

Moisture of the skin and perspiration definitely increase the susceptibility. The presence of moisture also increases the susceptibility to other irritants that are more soluble in oil than in water, *f. i.*, phenol or true mustard oil. In all these cases, the insolubility in water would favor the penetration into the more solvent skin. Marshall, Lynch and Smith, 1918, explain susceptibility along similar lines.

"Nitrogen Mustards" are somewhat less persistent than mustard gas, have about a fifth its potency, but are somewhat more rapid in action. The blisters heal in two to four weeks. All exposed tissues are killed. The eyes are especially sensitive. The inflammation may extend below Bowman's membrane and result in permanent blindness. The effects on the upper respiratory tract are similar to those of mustard gas, but there may be absorption from the lungs, and systemic effects: abrupt decrease of lymphocytes, agranulocytosis, necrosis of lymphoid tissue, destruction of the bone marrow, hemorrhagic lesions in the basal ganglia, miosis, flaccid paralysis of skeletal muscles, especially of the head and neck. The *treatment* is as for mustard gas.

Anticarcinogenetic Action.—It was feared that mustard gas burns of the skin would be followed by the development of carcinoma. This has not been so. To the contrary, the local application of 0.5 per cent in acetone checks the development of mouse and rat carcinoma and the tumors become necrotic (Berenblum, 1929, 1931; Visser and Vos, 1935).

Direct gastro-intestinal lesions occur by ingestion of the substance with the food or saliva. Animals that survive several days after being "gassed" in chambers generally have acute gastro-intestinal catarrh. The lesions are similar to those produced by local contact in other locations: superficial necrosis, followed by ulceration of the mucosa (Warthin and Weller, 1919). The gastro-intestinal symptoms in man are probably chiefly reflex, from respiratory irritation and shock.

The *kidneys* do not show direct changes, even with intravenous injection. Secondary involvement (cloudy swelling and hyaline casts) may occur during infection or extensive necrosis in severe local lesions. (Warthin and Weller, 1919). Such cases have diminished urine output, increased concentration, diminished urea and chloride. The condition improves on forced liquid regimen. Mild skin burns show no changes in the urine or blood (Hermann, 1918).

Fate.—The urine contains products of hydrolysis, probably dihydroxyethylsulfide, with all methods of administration. This is not irritant (Lynch *et al.*).

Destruction of Mustard Gas.—Dry hypochlorites chlorinate and destroy the substance readily, with evolution of heat "Bleaching powder" is useful as a "kill." Chloramine and dichloramine also react vigorously with "mustard." With these, the reaction appears to be more complicated, but the irritative qualities are destroyed. All chlorinating agents must be applied as concentrated and especially as dry as possible; else the immiscibility of "mustard" with water prevents intimate access of the chemicals.

Protection of the Skin against Mustard Gas.—The limited success of treatment makes prophylaxis especially important. The poison, like other fat-soluble irritants, is more injurious when the skin is moist; while oiling of the skin confers a certain degree of protection. Unfortunately, this protection is quite limited. It may be fairly complete for short exposure to low concentrations; with high concentrations it at least increases the efficiency of removal treatment. For long exposures, however, there is practically no protection by oils. Extensive experiments with different oils, ointments and admixtures revealed quantitative differences; but they are not sufficiently great to affect the practical results materially (Sollmann, 1919).

Removal of Mustard Gas from the Skin.—When the dichlorethylsulfide has penetrated the cells of the skin, the damage has been done, and treatment is only palliative. It is therefore imperative to remove the poison as completely as possible before it has penetrated and combined. The penetration is rapid and the fixation within the skin is almost as rapid, so that the efficiency of removal treatment is limited within five minutes, and almost nil after ten to twenty minutes. This, combined with the fact that most burns are not noticed until several hours after they were received, emphasizes the desirability of protection against exposure and contact.

The first step in the treatment of a mustard burn is the removal of the contaminated clothing. The removal from the skin may be attempted by chemical means or by solvents. The solvents have given better results, presumably because of their better penetration. Any convenient solvent may be used with almost equal results: alcohol, acetone, gasoline, kerosene, turpentine, oils or grease, petrolatum and somewhat less efficiently, soap. For practical reasons, chiefly economical, kerosene is generally preferred. The solvent treatment is materially more efficient if it is combined with rubbing, because this presses some of the poison out of the gland ducts.

Chemical Removal.—Chlorinated lime and the chloramines neutralize the poison if they are applied immediately; but they fail to reach any that has penetrated. This renders them inferior to the kerosene treatment. They would be useless five or ten minutes after exposure.

Treatment of Mustard Burns.—The various treatments that have been proposed involve mainly three principles:

1. *Attempts at chemical destruction of the poison within the skin* have been uniformly unsuccessful, since the poison is rapidly fixed within the cells and is out of reach of most, if not all, of the chemical antidotes.

2. *Protective measures* at least add considerably to the comfort of the patient, and may indirectly hasten healing somewhat. It is doubtful whether the natural course and healing of the burns can be materially influenced for the better by any treatment so far tried; but it can be materially influenced for the worse by irritation. Protective measures eliminate this additional injury. The patient should be removed from all chances of exposure to the poison, even to the dilute vapor, or other irritant vapors, until the burns are healed. Irritant dressings must be avoided.

3. *Antiseptics.*—The extensive raw surface, the lowered vitality and the presence of necrotic tissue in the blistered burns offer opportunity for infections; but the infection remains superficial and is easily kept in bounds by ordinary cleanliness. Most burns probably heal about the same whether antiseptics are used or not, but these should be given the benefit of the doubt. Antiseptics of the chlorine group have been found most serviceable, and should be used whenever possible (Warthin *et al.*, 1918). They are especially useful toward the end of the necrotic stage. Perhaps their benefit here may be referred partly to the solution of the necrotic tissue.

The comparison of different methods of treating the burns is not easy, partly because it is difficult to judge the severity of a burn and its presumptive course, especially if it was not followed through all its stages. Several adjacent blisters that look practically alike at the height of vesication may really be of a different depth; one may heal smoothly within two weeks, the other may undergo necrosis and require four weeks. Another source of error is the rather abrupt turning point when spontaneous improvement sets in. A necrotic surface that has been practically stationary for a week or more, starts to improve overnight, almost visibly. If treatment has been instituted within a few days of this turning point, it would naturally, but erroneously, receive the credit (Sollmann, 1919).

Treatment of Gastric Symptoms.—Nausea and vomiting are seen in a proportion of the intoxications by inhalation. Recovery generally follows without other treatment than a light diet. Occasionally the vomiting is very severe and prolonged. Such cases should be treated with alkalis, bismuth and milk diet, essentially like gastric ulcer.

There seems to be a general *lowering of resistance* after mustard gas poisoning, and therefore increased susceptibility to infections; influenza, bronchitis, pneumonia and tuberculosis (Warthin and Weller, 1919).

PHOTODYNAMIC ACTIONS

These interlock mutually with pharmacodynamic actions, since some chemical substances sensitize to actinic or ultraviolet light, especially through fluorescence, or light sensitizes toward these substances. Ultraviolet light also produces D vitamins from the cholesterol of the skin, and thereby acts on the calcium and phosphate metabolism. This effect is discussed under "Vitamin D" (see Index).

Dermal irritation begins to appear a few hours after exposure to the ordinary doses of actinic rays. It consists in hyperemia, followed by pigmentation, almost exclusively in the basal cells. These are stimulated to increased activity and quickened metabolism (review, H. Laurens, 1938). The amount of pigment formation is directly proportional to the preceding erythema in a given individual, but not in different patients (Rogin and Sheard, 1934). The erythemal sensitivity of the untanned skin differs not only for different persons, but for the same individual at different times. Erythema occurs in summer with one-half to two-thirds of the exposure required in winter, due probably to different moisture of the skin (review, W. W Coblentz, 1932). The sensitivity is increased by acid-producing food and diminished by alkali (Kittel and Stahl, 1933). The outer horny layer of the skin protects the true skin against ultraviolet rays by reflecting or absorbing them in great part, transmitting chiefly the other light rays (Laurens, 1936). Exposure of the *eyes* to ultraviolet radiation ordinarily causes conjunctivitis and blepharitis, but if excessive, the damage may progress to corneal erosion and, if long continued, to scotoma (Laurens, 1938).

Therapeutic Uses.—The stimulation and hyperemia of the skin by ultraviolet irradiation are utilized in dermatology, especially against psoriasis, superficially situated bacterial infection, sluggish ulcers and lupus vulgaris. Skin tumors have been produced in rats and mice by prolonged exposure, but far beyond the amount used therapeutically (Luce and Clausen, 1938, review).

Protection against ultraviolet radiation and sunburn has been investigated by Luckiesh *et al.*, 1946. They found dark red petrolatum the most effective agent for excluding the ultraviolet rays of natural sunlight which are chiefly responsible for the erythema. Addition of 10 per cent of phenyl salicylate would render this even more effective, and is harmless. Of insoluble powders, titanium dioxide gives the best protection; calamine is fairly efficient.

Distant Effects.—Zedda, 1933, reported that ultraviolet irradiation increases the *urine flow* and sodium chloride output, sometimes to three times the normal control period. It has also been reported that it raises the platelet count in idiopathic hemorrhagic *purpura.*

Bacteria may be killed or attenuated, but their susceptibility varies. Actinic rays are effective only through thin layers. Good results are reported for droplet disinfection of operating rooms (D. Hart, 1937). *Ferments* may be stimulated, inhibited or destroyed.

Photodynamic Sensitization.—Living cells may be sensitized by certain chemical substances so that they react to the luminous rays of the spectrum as to the ultraviolet. Most sensitizers are fluorescent, but sensitization is not due to fluorescence as such. Photodynamic effects require the presence of oxygen, which is not necessary for direct ultraviolet reactions (review, F. H. Blum, 1945). The photodynamic sensitizers include erythrosin, rose bengal, rhodamin, anthracene, acridine dyes, methylene blue, quinine, chlorophyll, hypericin, buckwheat, porphyrins (Laurens, 1938; F. P. Mathews, 1937). Photodynamic dyes also sensitize to heat (A. C. Giese and Crossman, 1946). Porphyrin sensitizations have clinical significance (see Index).

Paramecia are not harmed by the acridine 1:20,000 if kept in the dark, but die in an hour in diffuse daylight, and in six minutes if exposed to direct sunlight.

Frog's sartorius muscle suspended in Tyrode solution contracts when exposed to ultraviolet light; after a few minutes this is followed by relaxation and finally by rigor. The effects require the presence of calcium (Azuma, 1927). The contraction occurs in ordinary light if the muscle has been immersed for two hours in 0.004 per cent of hematoporphyrin, or in eosin or rose bengal (Lippay, 1927).

Perfused turtle heart is arrested by hematoporphyrin if exposed to light. This is not due to the formation of a toxic substance, for a second heart perfused in the dark with the perfusate of the first heart is not affected (Rask and Howell, 1928). The effect of porphyrins on *excised intestines* was investigated by Reitlinger and Klee, 1928.

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STOMACHICS

This term is applied to remedies intended to improve the functions of the stomach: either to increase appetite, especially by bitters and condiments, or to decrease gastric distress of various kinds, chiefly by carminatives. These also secure the expulsion of gas from the alimentary canal. *Simple bitters* generally contain some "*bitter principle*"—neutral substances, often crystalline, non-nitrogenous, sometimes glucosidal, and without pronounced systemic actions. In *aromatic bitters* these are mixed with volatile oils. The *astringent bitters* contain tannin. *Condiments,* which also contain aromatic oils or other sharp principles, form the transition to *carminatives.* Bitter, aromatic and "*sharp*" drugs have been used since antiquity as "tonics," and in functional dyspepsias. About a tenth of the medicines mentioned by Hippocrates belong to this class, and they have played a prominent role in folk medicine.

CARMINATIVES

These are aromatic and pungent drugs, used in flatulence and colic, to expel gas from the stomach and intestines, and to diminish the "griping" pains. Given by mouth or by enema, according to the situation of the gas, they may be promptly effective; in other cases they fail. They have a "warm" taste, and exert a mild irritant action on the digestive tract. The most useful carminatives are mints, fennel and anise; ginger; and capsicum.

Gastric Motility.—In normal human subjects peppermint oil or spirit temporarily inhibits the *hunger contractions*, but inhibition is followed by stimulation and regularization of the peristalsis, with slow and deep waves (Todd, 1930). The emptying time after meals is materially shortened, especially after fats (Sapoznik *et al.*, 1935). The acid secretion of the stomach in response to alcohol and histamine and in gastric ulcer is decreased by peppermint (J. Meyer *et al.*, 1935).

In unanesthetized trained dogs, carminatives relax the gastric tonus for five to thirty minutes, while the tonus and peristalsis of the intestines and colon are increased (Plant and Miller, 1926). With laparotomized animals the movements may be either increased or decreased (Gunn). The excised stomach is also relaxed. Relaxation of the cardial sphincter may be an important factor in the relief of gastric flatulence. "*Heartburn*" and retrosternal pain is associated with continuous stretching of the lower esophagus. It is overcome by the passage of peristaltic waves over this region, and may become more intense during the relaxation that follows the contraction wave (Payne and Poulton, 1928). The pain of gastric and duodenal ulcer is due partly to direct irritation of the denuded nerves, but largely to pyloric or duodenal contractions which may be excessively strong, or act on hyperexcitable pain endings.

Intestinal Motility.—Dilute suspensions or saline solutions of the carminative oils increase the tonus, rhythm and peristalsis if they are injected into the intestines of unanesthetized dogs, by a long Thiry-Vella loop. This would result in the propulsion of any gas. Occasionally the stimulation is followed by decrease of movement, which may be helpful in relaxing spasms, and explains the clinical use of carminatives to diminish the griping of irritant cathartics.

The carminative stimulation is abolished by cocainization, so that it is perhaps a sensory reflex (Plant, 1920). Excised intestines and those of laparotomized animals are relaxed (Gunn, 1921).

The antiseptic action of aromatic oils may be useful in gastric dilatation and intestinal putrefaction. The effects of peppermint, fennel and chamomile on the course of *inflammations* have been studied by W. Arnold, 1927.

Menthol and Peppermint Oil on Bronchial Foam.—McGuigan, 1921, found that these diminish the foaming of blood, saponin, etc., and suggests that their mechanism in catarrhs consists in breaking down foam in the air passages, and thus enlarging the effective lumen. However, the mucus of catarrh is not always foamy, especially not in rhinitis or pharyngitis, in which menthol gives most relief. The benefits are probably due to detachment of adherent mucus by the fresh secretion which follows the counterirritation.

PREPARATIONS.—***Peppermint Spirit,** U.S.P. (Spt. Menthae Piperitae; Peppermint Essence), is a 10 per cent solution (in alcohol) of *Peppermint Oil*, the vol. oil distilled from the fresh overground parts of the flowering plant of *Mentha piperita*, macerated with 1 per cent of peppermint leaves. The dose of the spirit is 0.3 to 2 cc., 5 to 30 minims. Analogous preparations are made from *Spearmint*, U.S.P., Mentha Viridis (Mentha spicata). Spearmint Oil contains not less than 50 per cent of carvone. The dose of *Spearmint Water*, U.S.P. (Aq. Menthae Viridis), a sat. watery solution of the oil, is 15 cc., 4 drachms; the *dose of the oil* is 0.1 cc., 1½ minims, on sugar.

Fennel Water, U.S.P., a saturated watery solution of *Fennel Oil*, U.S.P., distilled from the dried ripe fruit of Foeniculum vulgare. The dose of Fennel Water is 15 cc., 4 drachms.

Ginger, U.S.P. (Zingiber), is the dried rhizome, with outer cortical layer removed, of Zingiber officinale (*Jamaica Ginger*). Dose, 0.3 to 1 Gm., 5 to 15 grains, as powder or *Fluidextract*.—*Asarum* (Wild Ginger), *Galanga* and *Zedoaria* are similar to ginger.

BITTER STOMACHICS

Bitter substances when taken in moderate amount shortly before eating may improve deficient appetite, and the flow and quality (acidity) of the gastric juice, in conditions of poor health (anemia); although they have no effect on normal individuals (Carlson and coworkers, 1914 and 1915). The *mechanism of the action* of the "bitters" has not been demonstrated. It is conceivable that they act as a "chemical dinner bell," setting up a "conditioned reflex" of appetite. The aromatics and condiments probably act by mild direct irritation of the gastric mucosa, the beneficial effects being due to the hyperemia and motor stimulation.

Effect in Experimental Cachexia.—In dogs provided with a Pavlov gastric pouch, and rendered cachectic by repeated large hemorrhages, Moorhead, 1915, found that the administration of bitters improved the appetite and the gastric deficiency, although not quite to normal. The animals consumed more food and the gastric juice became more abundant and more acid. The increase of appetite occurred whether the bitters were given by mouth or by stomach; the increase of secretion was confined to oral use. The improvement occurred with the first administration, so that it was not due to the establishment of a habit. Possibly the bitter taste enhances the taste of foods, by contrast.

Experiments on Normal Individuals.—Ivancevic and Kadruka, 1938, report from roentgenologic observations on man that gentian causes swelling of the gastric mucosa and increased secretion, similar to normal digestive hyperemia. The effects are maximal in twenty to thirty-five minutes. Carlson and co-workers, 1914 and

1915, could find no beneficial effects in normal men or dogs. Therapeutic doses of bitters, however given, had no immediate or delayed effect on gastric secretion. When taken by mouth (or large doses introduced directly into the stomach) they inhibit the normal hunger contractions and the sensations of hunger, just as do other irritant or disagreeable substances.

Gastric Secretion.—Carlson, 1915, tested the effects on a man with gastric fistula, and on dogs with Pavlov miniature stomachs. The bitters were placed in the mouth, or directly in the stomach, before, with, or without food, etc. However the experiments were varied, the results were uniformly negative. This disposes of the rather contradictory results of older investigators as to direct secretion and "psychic juice." The introduction of irritant substances into the mouth also fails to provoke gastric secretion in man (Carlson, 1915).

Absence of "Taste" in the Stomach.—Albertoni and Tullio, 1912, found on a human subject that the direct introduction, through a gastric fistula, of bitter or sweet substances or bouillon, produced only the same immediate sensation as saline; but bouillon, bread or alcohol provoked speedier secretion of acid and, taken with food, afforded a more satisfactory sensation.

Pancreatic secretion and bile flow are not increased by bitters. Intestinal juice is first diminished, then increased (Reichmann, 1888; Jodlbauer).

Effect on Absorption.—Bitters are claimed to hasten the absorption of sugar and peptone from the stomach (Brandl, 1893), but seem to delay it somewhat from the intestine (Rieder, 1910).

Sojourn of the Food in the Stomach.—According to Heubner, this is shortened by small, delayed by large, doses. W. E. Morse found that *tabasco sauce* does not modify the discharge of water from the stomach.

Effect on Digestive Ferments.—Most of the bitters have no effect on digestion *in vitro*.

Antiseptic Action.—Bitters and aromatics are antiseptic and may influence digestion favorably by limiting putrefaction and abnormal fermentation.

Leukocytosis.—Bitters and aromatics *increase the leukocytes* of the blood (Hirt, 1856; Binz, 1875; Pohl, 1888). It has been claimed that these play a role in intestinal absorption (Hofmeister, 1887).

Therapeutic Uses of Stomachics.—These are employed: (1) To increase appetite, from whatever cause this be deficient. (2) To improve digestion in all kinds of "atonic" dyspepsias, with motor or secretory deficiency. They tend to remove the anorexia, oppression, constipation and hypochondria. The astringent bitters may be more useful in subacute or chronic gastritis, otherwise they are rather objectionable. Tannic acid must be especially avoided when the bitter is to be prescribed with iron, since this makes an unsightly mixture. The simple bitters and the majority of the aromatic bitters are tannin-free. (3) As tonics in anemia, convalescence, phthisis, to hasten reconstruction. (4) As antemetics. (5) To modify or improve the taste of food or medicines; and to obscure any "bad taste in the mouth."

Administration.—Stomachics should be taken within a half an hour, preferably five or ten minutes, before meals. They are generally more pleasant, and therefore more effective, if they are judiciously blended, as in the aromatic and compound bitters such as Compound Tincture of Gentian or of Cardamom. Overdoses produce nausea and so defeat their object. Since the effects of bitters involve the taste, it is probably useless to administer them in the form of pills and tablets, although this is often done.

SIMPLE BITTERS

These are practically free from aromatic oils or tannin, and can therefore be mixed with water. The tinctures are strongly alcoholic. Gentian is perhaps the most agreeable of the simple bitters. The Compound Tincture of Gentian is an aromatic bitter. Strychnine and quinine are often used in small doses for their bitter effect.

Gentian, U.S.P., the dried rhizome and roots of Gentiana lutea, is one of the most useful simple bitters. It is mentioned by Pliny. The bitter principles are glucosides Tannin is present in small amount—not astringent, but incompatible with iron. It is generally prescribed as the ***Compound Tincture of Gentian**, containing 10 per cent of gentian, aromatized with bitter orange and cardamom, in 45 per cent alcohol. Dose, 4 cc., 1 drachm. *Quassia*, the wood of Picrasma excelsa, or of Quassia amara, has an intense and disagreeable bitter taste. Dose, 0.1 to 0.5 Gm., as infusion or *Tincture*, 10 per cent. A 1 to 5 per cent infusion is used by enema (to ½ pint, retained as long as possible) against oxyuris. It is a rather ineffective insecticide (McIndoo and Sievers, 1917). The systemic effects of quassin have been studied by Antonibon, 1927.

Other Simple Bitters include: *Berberis*, the dried rhizome and roots of species of the section of Mahonia of the genus Berberis (pharmacology studied by Hilderbrandt, 1907); *Calumba* (Colombo), the dried root of Jateorrhiza palmata (pharmacology studied by Biberfeld, 1909); *Xanthoxylum*, the dried bark of Xanthoxylum americanum, or of X. Clava-Herculis; and *Pareira*, the root of a Chondodendron species. Commercial "Bebeerine sulfate cryst." is isobebeerine, obtained from Pareira. It is isomeric with codeine, and like this has narcotic actions (Scholtz and Koch, 1915). *Taraxacum* (Dandelion) consists of the dried rhizome and roots. Its composition was investigated by Power and Browning, 1912. The extract was reported to stimulate the bile flow in rats (Bussemaker, 1936).

ASTRINGENT BITTERS

With these, tannic acid is a prominent ingredient, whilst volatile oils are present only in small quantity, if at all. The preparations can be mixed with water.

Cimicifuga (Black Cohosh, Black Snakeroot, Macrotys), the dried rhizome and roots of Cimicifuga racemosa. Dose, 1 Gm., 15 grains. The constituents were investigated by Finnemore, 1910. It contains a resin, cimicifugin or macrotin. It has been employed as stomachic, against chorea, and as "uterine tonic." Extensive pharmacologic study failed to reveal any distinctive effects, except some depression of excised intestine and uterus, probably by the volatile oil (D. I. Macht and Cook, 1932)—*Condurango,* the dried bark of Marsdenia Cundurango. Dose (of the fluidextract), 1 to 4 cc.—*Cusparia* (Angostura Bark), the dried bark of Cusparia febrifuga. Dose, 0.6 to 2.5 Gm.—*Serpentaria* (Virginia or Texas Snakeroot), the dried rhizome and roots of Aristolochia Serpentaria, or A. reticulata. Dose, 1 Gm.

AROMATIC BITTERS

These contain both aromatic oils and bitter principles, but no tannin. Their alcoholic preparations turn turbid when mixed with water.

Aromatic bitters include: *Bitter Orange Peel,* U.S.P. (Aurantii Amari Cortex), the dried rind of the unripe fruit of Citrus Aurantium; used as the *Tincture,* U.S.P. (20 per cent), and in Compound Tincture of Gentian. Grapefruit contains a bitter glucoside *narginin.* Oranges contain the practically tasteless glucoside *hesperidin.* Addition of 1 per cent of these to the diet of rats produces no effect of any kind (R. H. Wilson and de Eds, 1940). *German Chamomile,* the dried flower heads of Matricaria Chamomilla (used as infusion, internally as stomachic, carminative and diaphoretic; externally as counterirritant in contusions and other local inflammations. The antiphlogistic constituent of chamomile oil is a blue hydrocarbon, *azulon,* $C_{15}H_{18}$ [Heubner and Grabe, 1933]. Dose, 15 Gm., 4 drachms). *English or Roman Chamomile,* the dried flower heads of Anthemis nobilis; *Calamus* (Sweet Flag), the peeled dried rhizome of Acorus Calamus; and *Ginseng,* the dried root of Panax quinquefolium, highly valued by the Chinese. Korean ginseng contains a glucoside said to lower blood sugar in various hyperglycemias (Abe and Saito). Other species of Panax and Aralia are also aromatic bitters. Numerous other bitters are used in domestic medicine.

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CATHARTICS

Cathartics, purgatives or evacuants are drugs which induce defecation They may do so by increasing the bulk of the intestinal contents (petrolatum, agar, etc.), by preventing the absorption of water (salines), or by irritating the small or large intestine, as most of the vegetable cathartics. Their irritation is is relatively mild and is confined more specifically to the intestines, by selective action, or because the alkaline reaction or bile of the intestines favors their solution or decomposition. This solution should not be too rapid or the drugs will be largely absorbed or decomposed before reaching the lower intestine. The isolated principles are therefore less useful, and sometimes less effective than the galenic preparations in which they are masked as compounds or by the extractives of the drug

Liberation and Solution of the Cathartic Constituents.—Castor oil and croton oil become active only when their fatty acids are liberated; croton oil contains some free acid and is, therefore, pustulant also on the skin. The emodin cathartics often contain glucosidal compounds, which must be split before the action occurs. The "resins" are insoluble in water, but are decomposed and dissolved by alkalis and bile.

Influence of the Bile on Cathartics.—The *bile* seems to be necessary for the activation of many of the resinous cathartics, the following being relatively or quite ineffective in its absence: gamboge, podophyllum, convolvulin, jalap, and scammonium (Buchheim and Stadelmann). The bile acts presumably by increasing the solubility. Rhubarb, senna and calomel are active in the absence of bile (Valeri, 1910). Aloe seems to act quite well without bile in animal experiments; but clinically it has been claimed that it is ineffective in biliary obstruction.

Toxic Effects.—The vegetable cathartics are not corrosive. Even the drastic cathartics do not ordinarily produce inflammation, because they are expelled rapidly; but if their propulsion is prevented by obstruction, or slowed as by opiates, they may lead to enteritis, especially colitis, and to nephritis. The intestinal irritation may also become cumulatively harmful if the irritant cathartics are used habitually.

The *location of action* may determine the choice of the cathartic. The emodin cathartics (senna, etc.) act mainly on the colon. Castor oil stimulates peristalsis in the small intestine. Colocynth increases the movements of the small intestine and leads to intestinal effusion. Magnesium sulfate quickens the passage through the small intestine, and prevents the absorption of fluid and the concentration of the contents of the large intestine. Calomel increases peristalsis both in the small and large intestines.

The older investigations have only a limited value, because they generally involved operative procedures which are likely to render the intestinal movements abnormal or to arrest them altogether. Cannon's method of observing these movements in intact animals by means of the roentgen rays opened the way for more reliable observations. This method was first applied to pharmacologic problems especially by Magnus, 1902, and by his pupils. Their results have been confirmed in man (*f. i.*, Meyer-Betz and Gebhardt, 1912). Another fruitful method, which has been applied especially by Lenz, 1923, consists in replacing a part of the abdominal wall by a plate of transparent celluloid, which heals into the wound and serves as a window. This has been modified by Barcroft and Robinson, 1929, into "exteriorization" of the intestines. Thiry-Vella fistulas permit recording of observations by sounds (the optimal conditions are described by C. M. Gruber and Anthony, 1935) and by bolus-progression (Quigley and others). The phenomena in animals correspond in general to those in man (Alvarez, 1929).

The *defecation reflex* is started by the arrival of the mass in the rectum. It is greatly influenced, however, by the sensitiveness of the rectum and by the habits of the patient. It is here that the delay in constipation mainly occurs.

A tonic mechanism for the rectum is located in the midbrain, and the rectal stretch reflexes are lost after low section of the medulla (O. R. Langworthy and Rosenberg, 1939). Defecation usually involves a reflex through the spinal cord; but destruction of the lumbar and sacral cord results in diarrhea, lasting several days, followed by normal evacuation of the large intestine at the customary interval (Goltz and Ewald, 1896). The intra-intestinal mechanism can therefore control defecation, if necessary (Schüller, 1911). (Review of defecation reactions, Lehmann, 1912.)

The anthracene and resinous cathartics and the phenolphthaleins also increase peristalsis if they are injected *subcutaneously or intravenously;* the resin group is even more active by this channel. The action may even then be local, the constituents being excreted into the intestine by bile. The cathartics are not administered in this manner, in practice, since the injection would be painfully irritant; the effects are also more easily controlled when the drugs are given by mouth.

The *effectiveness of cathartics for animals* differs materially from that in man. The relations are discussed by Fuehner, 1925; as also the evaluation on mice. The response of dogs and cats is much more closely akin to the human than is that of rabbits. The small crustacean *Daphnia* has been proposed for the essay of cathartics; its suitability appears inherently doubtful; the technic is described by Tinsley, 1938.

Cathartics on Excised Intestines.—The effects are not related to those produced in life. For instance, the addition of aloin to the bath is inactive; cascara and castor oil inhibit the contractions; saponified croton oil stimulates (Meissner, 1916). Alvarez and Taylor, 1917, obtained more positive results by giving cathartics to living rabbits, then excising the intestines. The segments showed irregular irritability. The doses were so high, however, that the significance of the results is doubtful. The reactions of *inflamed intestines* are described by Tsurumaki, 1928.

Time of Action.—A cathartic which acts on the large intestine can not produce the effect until it reaches this place. Even then the response depends on the habits of the patient. These become less important with the more irritant cathartics. The usual time of response, for the more important cathartics, is as follows: *Salines*, one-half to one hour on empty stomach; two to four hours if in bed. *Castor oil*, one to two hours on empty stomach. *Jalap*, three hours or less. *Senna*, four to five hours. *Rhubarb* or *Phenolphthalein*, four to eight hours. *Cascara* or *Aloes*, eight to twelve hours. *Podophyllum*, ten to sixteen hours.

Colic or *"griping"* is proportional to the severity of the irritation and is due partly to direct irritation, as evidenced by abdominal tenderness, but chiefly to strong and spasmodic peristalsis, especially without preceding relaxation wave and therefore against excessive resistance, resulting in forcible distention. It may also result from interference with the blood supply through vascular spasm, arteriosclerosis or embolism. It is essentially similar for all smooth muscle, as in the labor-pains of the uterus, overdistention of the urinary bladder, and renal or biliary colic. Gastro-intestinal colic may be mitigated by carminatives, amyl nitrite, atropine or heat externally or internally. Colics may be completely inhibited by ether or chloroform anesthesia. Tonic spastic contraction without distention, such as occurs under morphine and in the spastic colon of nervous constipation, generally does not give rise to pain.

Consistency of the stools varies from the soft but formed stools of the milder laxatives, to the watery stools of the "hydragogue" cathartics, the salines and drastics. The more rapid passage of the intestinal contents leaves less time for the *absorption of fluid*, so that the stools contain more water. Some of the cathartics also prevent the absorption of fluid by osmosis (salines); or by imbibition (agar); and some perhaps by inhibiting the absorbing power of the epithelium (castor oil, calomel). The fluid in these cases comes really from the food rather than from the body. Even large doses of the anthracene cathartics (senna, cascara, etc.) do not increase the secretion of intestinal fluid (Thiry, Brieger, Flemming). On the other hand, the irritant cathartics (colocynth, jalap, etc.) actually produce *effusion* into the small intestine. The tissue dehydration is the same, whether they are deprived of fluid by effusion or by nonabsorption.

Catharsis is likely to be accompanied by some *intestinal hyperemia*, were it only by the increased intestinal movement. The irritant cathartics produce more violent intestinal congestion, which extends also to the pelvic organs, and may perhaps increase the menstrual flow. *The systemic circulation* is affected indirectly by the splanchnic dilatation and by the withdrawal of fluid from the blood. Both factors tend to lower the blood pressure moderately. The heart rate is slowed reflexly (C. H. Neilson and Hyland, 1913).

The following gives a useful **clinical classification**; but the effects vary with the dose. The more important agents are in italics.

1. **Laxatives or aperients** increase peristalsis only moderately, producing somewhat more frequent stools, of almost normal consistency, and this without causing notable irritation. They are active in *doses* of 10 Gm. or over.

Fruits, Manna, Agar, etc.; mechanical means (massage, *enemas*, etc.); Sulfur, *Magnesia*, Carminatives, Bile, Bland Oils (*Olive*, Cottonseed, *Liquid Petrolatum*, etc.). Small doses of Cascara, Senna, Castor Oil, Rhubarb, and Ipecac are also laxative.

2. **Purgatives** increase peristaltic activity, causing more frequent soft or semifluid stools.

(*A*) *Simple Purgatives.*—Active in *doses* of 0.2 to 1 Gm. Full doses may cause more or less colic and irritation: Aloes, Rhubarb, Senna, *Cascara*, *Phenolphthalein*, *Castor Oil*, *Calomel*, small doses of drastics.

(*B*) *Saline Purgatives.*—Active in doses of about 10 Gm. Rather profuse, watery stools, with practically no irritation or griping: *Sulfate of Magnesium* or Sodium Phosphate, Magnesium Citrate, Potassium Bitartrate, Rochelle Salt, etc.

3. **Drastics** produce watery stools, with much irritation. Large doses are liable to set up an enteritis: Elaterium, Colocynth, *Jalap*, Scammony, Gamboge, *Podophyllum*, Croton Oil, the stronger Mercurials and Antimony Sulfide.

4. **Hydragogues** are all which produce watery stools, *i. e.*, the salines and drastics.

5. **Cholagogues** were supposed to increase the bile flow: *Aloes*, Rhubarb, Mercurials, Podophyllum, Euonymin, Sod. Salicylate or Phosphate, Acid. Nitrohydrochlor. Dilut., Bile.

Therapeutic Indications.—Cathartics are used chiefly for the following indications: (1) *To relieve constipation*—cascara, rhubarb, phenolphthalein, small doses of salts. (2) *To soften the stools*, in hemorrhoidal and other rectal diseases, and to prevent straining in aneurysm, hernia and apoplexy—petrolatum, cascara, agar, mucilaginous drugs. (3) *To cleanse the intestines* in digestive disturbances, diarrheas and other intestinal putrefactions—calomel, castor oil, rhubarb, cascara, aloes. (4) *To facilitate the absorption of dropsies; to relieve the kidneys in nephritis; to relieve internal congestions*, especially of the brain—calomel, large doses of salines, compound jalap powder.

Cathartics are among the most ancient methods of internal medication, and were for a long time practically the only method. The Greeks used the same word, *φαρμακειν*, both for intestinal medication in general and for the use of cathartics in particular. The present English word *physic* is similarly applied.

The annual consumption of cathartics in the United States was reported (1933) as twenty million pounds.

Contraindications.—All inflammatory conditions of the abdominal organs (appendicitis, peritonitis, gastro-enteritis, etc.) contraindicate intestinal irritants. Pregnancy and menstruation are contraindications to the use of the stronger cathartics, since the hyperemia may lead to abortion or excessive menstrual flow. General debility, tendency to collapse, threatened intestinal hemorrhage and toxic spasm of the intestine are further contraindications. Cathartics must not be used in intestinal obstruction or intussusception.

Cathartics should be used rather sparingly in the chronic intestinal stasis of *habitual constipation*, the condition being treated most effectively by the removal of the cause and the cultivation of proper hygienic and dietetic habits, aided by the mechanical laxatives, liquid petrolatum, agar or enemas. Small doses of salts, cascara or similar aperients may be needed. The irritant cathartics should be avoided. The fatality rate of appendicitis is much higher for patients who have been in the habit of taking laxatives (J. O. Bower).

Pharmacologic Classification.—From the standpoint of the mechanism of action, cathartic agents may be grouped as: (1) *Parasympathetic stimulants*, pilocarpine, physostigmine, choline, etc. These produce toxic side actions and intestinal spasm, so that they are not used as cathartic therapy; but physostigmine and prostigmine are employed against postoperative intestinal gas distention. (2) *Muscular stimulants,* acting more directly on smooth muscle. Barium is effective but too dangerous; histamine and extract of posterior pituitary gland are of inconstant efficiency; but posterior pituitary is employed in gas distention. (3) *Capillary poisons* are concerned in gastro-enteritis, and violent catharsis of specific bacterial toxins, toadstools, anaphylaxis, and in the toxic effects of certain drugs, colchicum, arsenic, mercury and other metals. The agents of these three groups are discussed under the individual drugs (see Index). (4) *Mechanical distention by retention of intestinal fluid* produces softened stools to copious watery evacuations, without inflammatory injury. The degree of distention may be graded by the choice of the agents and by the dosage.

(a) **Saline cathartics** are easily soluble but difficultly absorable salts, which retain fluid in the intestines by their osmotic pressure. The distention of the duodenum and upper ileum arouses increased motor activity throughout the intestines, resulting in a prompt laxative effect. When the unabsorbed salt solution itself reaches the colon, it may cause purgation by direct distention, or smaller quantities may be merely laxative by hindering inspissation of the contents. Saline cathartics are used to evacuate fluid in dropsy; they have occasional use in constipation; but the intestinal movements which they induce are not of the normal type of peristalsis and they should not be used habitually. Intestinal colic, as that of lead poisoning, offers a special indication for magensium salts, for these resolve the spasm by direct depressive action on the intestinal muscle. Magnesium oxide and carbonate are also used to neutralize gastric hyperchlorhydria, which may be a cause of constipation. Further details are considered under the individual salts (see Saline Cathartics in Index).

(b) **Mucilaginous drugs, agar, psyllium seeds, bran and prunes** are also unabsorbable and retain moderate quantities of fluid by imbibition, thus modifying the bulk and consistence of the feces, so that these are more easily expelled. They are useful in habitual constipation, especially if aided by the occasional administration of cascara. They have some advantage over mineral oil in that they do not interfere with the absorption of vitamins and do not cause leakage, but they are less convenient to regulate.

***Agar,** U.S.P. (Agar-Agar), is a dried mucilaginous substance extracted from marine algae growing along the eastern cost of Asia. It consists mainly of the hemicellulose "gelose," which gelatinizes with water. It is tasteless and has been used for culinary jellies, but is not digested (8 to 27 per cent is utilized in man; Swartz, 1911; herbivorae utilize about 50 per cent; Lohrisch, 1908). It was introduced as a laxative by A. Schmidt, 1905. The dose is 4 to 15 Gm., 1 to 4 drachms, of the chopped shreds or powder, with breakfast cereal. It may also be boiled with the cereal or made into a jelly (1:200 boiling water). The effect is usually not noticeable for nearly a week. The efficiency is not great, and it usually requires the addition of cascara or phenolphthalein.

Psyllium consists of the seeds of a plantain, Plantago Psyllium and related species, of Southern Europe. Its hull contains a mucilaginous substance which swells to a jelly in water. The laxative dose is a teaspoonful to a tablespoonful of the seeds. It may cause fecal impaction and lesions in the lower intestines. In rats and dogs it may produce a peculiar pigmentation of the kidneys, but this does not appear to interfere with renal function (Thienes and Hall, 1939). Its dose is 4 to 15 Gm., one to three times daily. It may be administered in orange juice. *Bran* probably owes its laxative action to water-imbibition, not to mechanical irritation or to any soluble constituent (M. B. Davis, 1931). Its richness in vitamin B complex is useful when this is deficient (Report. Council on Foods, 1936, J.A.M.A., *107:* 874). In many individuals it irritates the intestinal mucosa, and in spastic constipation it may increase the spasticity and lead to obstruction, especially if the dosage is increased when small doses are not effective (Davis, 1931). Roentgenoscopic studies show little effect on the normal events in the intestines except that the emptying time is shortened by its daily use in about a fourth of normal individuals. It relaxes haustral hypertonus (Fantus, Kopstein and Schmidt, 1940). *Prunes* act partly by imbibition, but they also contain a directly laxative constituent, apparently related to dihydroxy phenyl isatin (G. A. Emerson, 1933). *Other fruits* act as laxatives chiefly by their organic acids and sugars. *Tamarind,* the fruit of Tamarindus indicus, owes its activity to organic acids, especially citric. It is used as a laxative, in doses of 4 to 30 Gm. (1 to 8 drachms). *Manna,* the dried saccharine exudation of an ash tree, Fraxinus ornus, contains about 90 per cent of mannite, a difficultly absorbable sugar, which is laxative by osmosis. Its dose is 15 Gm., 4 drachms, to 60 Gm., 2 ounces, as infusion. *Karaya gum* produces serious intestinal lesions when fed to rats in large quantity for long periods (Hoelzel *et al.,* 1941). Rats receiving more than 20 per cent of *inulin* with their diet develop severe diarrhea (Hodge, 1944).

Methylcellulose ("*Methocel*") has been suggested as a synthetic hydrophilic laxative. It is a white fibrous material, dissolving in cold water to a clear jelly which coagulates on heating and redissolves on cooling. It is insoluble in most organic solvents. It is nontoxic by mouth, is not absorbed from the digestive tract, and does not interfere with the absorption of fat-soluble vitamins. Five grams twice daily increase the water content and bulk of the stools by about ten times the weight of the drug (M. L. Tainter, 1943). It is not metabolised and does not increase the methanol or formic acid content of the urine (Machle *et al.*, 1944). Large amounts fed to rats over long periods have no deleterious effects on the normal growth curve (Lehman and Yonkman, 1944). **Ethylcellulose** ("*Ethocel*"), which is insoluble in water and soluble in organic solvents, is also innocuous (Deichmann and Wintherup, 1943). **Cellulose acetate phthalate** likewise appears inert. Growth curves of rats remain normal when 20 per cent is added to the diet; above this there is some mechanical interference with food disposal, without other symptoms or lesions. Dogs remain in good health when fed 16 Gm. daily (Hodge, 1944). The substance appears promising for "enteric" capsules or coatings, as it is insoluble in acid fluids, and quickly soluble in alkaline. Roentgen studies on normal men indicate that the capsules disintegrate within eight hours, generally in the intestines, exceptionally in the stomach (Hodge *et al.*, 1944).

(c) **Mineral Oil,** which is not absorbed from the intestines (except minimal quantities, Channon and Collinson, 1929), prevents inspissation in the colon and is therefore used as laxative, especially in habitual, nervous and spastic constipation, and to prevent straining at stool in cardiac decompensation, and in hemorrhoids, where it also protects against irritation. It hinders the absorption of lipo-soluble drugs, bile and vitamins, such as carotene, especially if taken at meal time. Ordinary doses consumed at other times do not interfere materially with the absorption of vitamin A (Dutcher, 1934; R. W. Jackson, 1934). Interference with absorption of vitamin A is much less than for carotene (Dutcher, Harris *et al.*, 1934); but addition of 5 per cent to the diet of rats raises their codliver oil requirement to three times (M. O. Smith and Spector, 1940). Excessive quantities of the oils which are not thoroughly incorporated in the feces are likely to leak insensibly from the anus. Emulsified oil is less liable to this and is more easily taken. The leakage and flatulence diminish with habitual use (F. T. Jung and Isaacs, 1939) (see Index, Petrolatum).

Evacuant Enemas.—Rectal injections or clysters increase the peristalsis of the large and small intestines in response to the mechanical distention. The effect is enhanced by the addition of irritants. Enemas have an *advantage* over cathartics taken by mouth, in that they may be made absolutely nonirritant, and may therefore be used in conditions in which the other cathartics are contraindicated. If the purpose of the enema be merely to *soften hardened scybala,* they would be used warm, in copious quantities, or as decoctions of mucilaginous substances. Olive oil is sometimes employed; it is less solvent, but if it is administered carefully in amounts of 70 to 500 cc., it can be retained several hours. To secure the maximum motor effect, the injection must be used cold, and in fairly large quantity: adults a pint, quart, or more; children according to age (at a year, an ounce, and about ½ ounce more for each year). *Irritants* may be added to enemas to secure immediate expulsion: soap, even a small quantity; molasses, 1:8; salt, 1:16; turpentine, 1:20 (emulsified with egg yolk), especially against flatulence; bile 1:50.

Enemas also have other uses: For *local effects* on the rectal mucous membrane (astringents, etc.); for the *removal of parasites;* and as a method of *introducing medicine and nourishment.* Irritant injections into the colon may either inhibit the emptying of the stomach, by pyloric spasm, or may shorten the gastric sojourn by increased peristalsis (F. W. White, 1917, x-ray method with cats).

Evacuant Suppositories.—A small plug of soap, or a Glycerin Suppository, U.S.P., evacutes the rectum promptly by sensory irritation, without distention.

IRRITANT CATHARTICS

Most of the "active purgatives" are irritants, but they differ greatly in degree and location. The latter depends partly on solubility. If they act high in the small intestines, the peristalsis is likely to be irregular and generally griping, with liquid stools; but calomel (see Index), which begins its action in the duodenum, is usually mild, with soft rather than liquid stools, because its solubility is limited. Bile (see Index) acts on the duodenum, but is mild, because the bile acids are reabsorbed so that the action does not extend far down. Sulfur (see Index) is also rather mild, as it must be converted into the sulfide. The other irritant cathartics may be grouped into the following groups: (1) *Those which act mainly on the colon and rectum* include the drugs containing emodin and other anthraquinone derivatives: Senna, cascara, rhubarb, aloes and perhaps also phenolphthalein. (2) *Those which stimulate peristalsis of the small* *intestine* and inhibit the antiperistalsis of the colon, without producing much irritation or effusion, include castor oil and probably calomel, bile and sulfur. (3) *Those which cause marked intestinal effusion and irritation* comprise colocynth, jalap and presumably the other drastic resinous cathartics, podophyllum, elaterin, gamboge and croton oil.

EMODIN OR ANTHRAQUINONE CATHARTICS

Senna, rhubarb, cascara, aloes and related drugs contain glucosidal compounds which are inactive as such, but are hydrolyzed or oxidized in the alkaline intestine, yielding various oxymethyl-anthraquinones, especially emodin and chrysophanic acid (Buchheim; Tschirch and pupils, 1899). These act chiefly on the large intestines, as laxatives, aperients or ecproctics, with easier defecation of formed stools. They are often more effective when taken in divided doses (three times daily) than as a single dose. With larger doses and with the more active members the action begins in the small intestines, with griping and forced evacuation of liquid stools; but it does not readily progress to inflammation. The effects are fairly easily controlled by grading the dosage, and by repeating the smaller doses, as the action tends to be cumulative. The dosage may be reduced or omitted when the desired degree is attained. These drugs are therefore used especially in chronic constipation, in addition to or alternation with mineral oil. Prolonged use tends to decrease the response of the intestines, so that the effect occurs only with larger doses which are liable to set up chronic inflammation of the mucosa. Cascara is the mildest of these drugs and the most easily controlled. Senna is the most active and generally causes griping and semiliquid stools. Aloe and aloin are intermediate, but can be pushed to drastic action which may result in abortion. Rhubarb catharsis is likely to be followed by constipation, which has been attributed to its tannic acid. *Emodin* (trioxy methylanthroquinone) is probably the most important constituent of this group. It is present in the amount of 0.8 to 1 per cent in senna; 2.6 per cent in frangula; 0.6 per cent in cascara; 0.8 per cent in Cape aloes; and 1.5 per cent in rhubarb (Tschirch and Hiepe). Chrysophanic acid (dioxymethylanthraquinone) is also important. Phenolphthalein acts similarly to cascara and aloes, but the response is variable. Its chemical structure is somewhat different.

The pure emodin substances would be too irritant, but their action is graded by their slow liberation and by the presence of colloid extractives. Numerous isomers are possible (fifteen for emodin alone). The special character of the different drugs is probably due to differences in these isomers, in the stability of their glucosidal combination, and to the presence of other associated substances (tannin in rhubarb).

Fate.—Emodin is partly absorbed and is excreted into the urine and milk (laxative effects on sucklings). The drugs containing emodin *color the urine* yellowish-brown when it is acid, reddish or violet when alkaline. It may be advisable to acquaint the patient with this fact.

Other drugs which change the color of the urine are: *Logwood* (Hematoxylon) does not color acid urine, but produces a reddish or violet color in alkaline urine. *Santonin* gives a yellowish color to acid urine, with a yellow foam; if the urine is made alkaline it gives a pronounced pink. *Picric acid* gives reddish-brown color in both acid and alkaline urine. The various *coal-tar products* give a brownish-black color. *Methylene blue* imparts a green color.

Manner of Action.—The older work (Buchheim; Tappeiner and Brandl, 1889) showed that the action of the emodin group is mainly on the large intestine, which reacts by increased movements also to intravenous injection; and that there is no increase of intestinal secretion. Aloe and podophyllum do not increase the *bile flow* in constipated patients (Ivy, Roth and Gutman, 1945). The x-ray experiments (Magnus, 1909; and Meyer-Betz and Gebhardt, 1912) and the observations through the abdominal window (Lenz, 1923) confirm that ordinary doses of senna do not accelerate the passage through the stomach and small intestine, but solely through the colon. With aloes the lower ileum participates somewhat. The normal peristaltic activity of the colon consists in the occasional formation of limited but firm contraction rings, which persist for some time, either stationary, or traveling slowly up or down the intestine. When these cathartics reach the colon, these contraction rings become much more frequent, tend to travel more rapidly downward, stripping the contents into the rectum.

The localization of this action in the colon is due partly to selective penetration, for anthropurpurin, *f. i.*, stains the mucosa of the colon much more intensely than that of the small intestine. It is possible that sensory reflexes participate. The cathartic effects of senna occur also on *intravenous* or *intramuscular injection*. Overdosage causes convulsions and vomiting (W. Straub and Triendl, 1937).

Susceptibility of Animals.—Rabbits are so refractory to anthraquinone catharsis that they are unsuitable for experimentation. Dogs can be purged, but are not very susceptible. Cats respond well. They require about the same absolute dose as man, 2 Gm. of senna, etc.

Observations of senna actions through an abdominal window were made by Lenz, 1923, by sewing a celluloid pane into the abdomen of cats and controlling the progress of the contents by radioscopy. Senna infusion was administered by stomach tube, with a meal. While the senna sojourns in the stomach, the gastric movements are barely stimulated; but within *eighteen to thirty-five* minutes, before the senna has left the stomach, strong peristaltic waves and a propulsive tonus ring start in the colon, which is normally in almost complete repose. This action—at a distance—lasts half an hour to an hour. There is little further action until the senna itself arrives at the colon, *about one and one-half to two and one-half hours after administration.* This causes immediate stimulation of the propulsive *colon peristalsis*, with inhibition of the normal retention-movements, the stationary or ascending tonus rings and antiperistalsis. Between *two and one-half to five and one-half hours* after administration, as more and more of the senna enters the colon, intensive tubular propulsive movements are set up, and lead to defecation of liquid stools, since there is no time for inspissation. The movements are so violent that defecation may be released from the proximal colon. The defecation is followed by tonic contracture of the colon, more powerful and more persistent than normal. This passes into relaxation of the colon and arrest of all its movements, for one or two hours; then the whole process is repeated, so that there may be four stools in three hours. When the senna has been entirely evacuated, the colon is immobile and remains so for hours. The *movements of the small intestines*, which in the cat are normally of the rosary type exclusively, are also replaced by tubular propulsive peristalsis during the passage of the senna, three and one-half to five and one-half hours after administration. They return to the normal type when the senna has been evacuated. *Emodin* has the same effects of senna; *anthraquinone* causes less stimulation of the propulsive movements and produces stimulation instead of inhibition of retention movements. The senna effects are prevented by anesthetizing the intestines with cocaine or procaine.

Vella fistulas permit observations on unanesthetized dogs. The effects of emodin, cathartics, phenolphthalein and podophyllin on the ileum are similar for intravenous injection and for instillation into the intestinal segment: generally a sudden decrease of tonus followed in two to ten minutes by increase of peristalsis. Atropine first increases, then inhibits the peristaltic stimulation (Gruber, Bryan and Richardson, 1932). With excised small intestines, kept in good condition by *perfusion through their blood vessels*, Carnot and Glenard, 1913, found that the injection of senna infusion, aloin or phenolphthalein into the lumen or vessels causes augmentation of peristalsis, spasm and evacuation. *In segments of excised intestine* suspended in saline solution, cascara increases the rate, but lessens the intensity of the contractions (Flury, 1912).

CASCARA SAGRADA

This is used chiefly in habitual constipation. It softens the stools without noticeable irritation. The susceptibility is not lost with use; on the contrary, the establishment of regular habits usually permits it to be gradually withdrawn. By its bitter taste, it acts also as stomachic. It may be given as the fluidextract, 15 drops three times daily; or in a single dose, a half teaspoonful, in the evening. This causes a single soft stool in the morning. In the Aromatic Fluidextract, which is much more pleasant, some of the bitter and cathartic principles have been destroyed (Wenzell, 1886). It may be given in twice the dose.

It is generally stated that the *fresh bark* is emetic, through the presence of a ferment which gradually disappears as the bark is aged. R. H. True and Klugh, 1909, did not find any emetic effect from the unaged bark. When cascara is administered *hypodermically*, its constituents are rapidly absorbed and excreted by the kidneys, producing renal irritation, but *not* catharsis (Chistoni, 1914).

Preparations.—*Cascara Sagrada*, U.S.P., is the dried bark of the shrub Rhamnus Purshiana, stored at least one year. Cascara sagrada ("Sacred Bark") was used by the early settlers, but was little known to the profession till introduced by Bundy, 1877. Johnson and Hindman, 1914, review its history, composition and bibliography. The active principles are: *Cascarin*, which is a cathartin or emodin principle, isoemodin, bitter resins, etc.; no chrysarobin or chrysophanic acid (Jowett, 1904, who claims that emodin is not the main active constituent). It is used as the ***Extract**, 1 Gm. of the powder representing 3 Gm. of the bark, dose, 0.15 to 0.5 Gm., 2½ to 8 grains. *Tablets of Cascara Sagrada Extract*, U.S.P.; the usual sizes contain 0.12, 0.2, and 0.3 Gm. of Extract. ***Fluidextract**, extracted with hot water, evaporated and mixed with alcohol to about 18 per cent; dose, 1 to 2 cc., 15 to 30 minims. ***Aromatic Fluidextract** (Aromatic Cascara), with the bitter principles partly destroyed by digestion with boiling water, flavored with glycyrrhiza extract, saccharin, anise and coriander oils and methyl salicylate; preserved with 18 per cent of alcohol, flavored with glycyrrhiza, aromatics and saccharin. Dose, 2 to 4 cc., ½ to 1 drachm. *Frangula* (Buckthorn Bark), the dried bark of Rhamnus frangula, is used similarly. *Rumex crispus* (Dock Root) is said to contain chrysophanic acid, about 0.1 per cent of an emodin identical with that of cascara (Beal and Okey, 1919).

SENNA

The effects are more extensive and more irritant than with the other drugs of the group, so that it is better suited for acute than for chronic constipation. There is considerable griping, which may be corrected by carminatives, or by the previous extraction of the resins with alcohol (as in the Fluidextract).

Preparations.—*Senna*, U.S.P., is the dried leaflets of Cassia species. Introduced by the Arabians. Constituents: senna-emodin, senna-isoemodin, senna-chrysophanic acid, and other anthraquinone derivatives (rhein, aloe-emodin), free and in glucosidal combinations; also some salicylic acid (Tutin, 1913, 1914; Tambach, 1913). Dose, 2 Gm., 30 grains. It may be administered as *Fluidextract*, U.S.P.; dose 2 cc.; or as the *Syrup*, U.S.P., 25 per cent flavored with coriander, dose 2 to 8 cc., ½ to 2 drachms. *Compound Senna Powder*, N.F. (Compound Licorice Powder), contains 18 per cent senna and 8 per cent sulfur, flavored with glycyrrhiza and fennel; dose, 4 Gm., 1 drachm. The obsolete *Compound Infusion of Senna* ("Black Draught") contained senna, magnesium sulfate and manna. The seed pods were also used (*Sennae Fructus*, B.P.). *Cassia Pulp*, B.P., is an evaporated watery extract of the ripe fruits of Cassia Fistula. Dose, 4 to 8 Gm., 60 to 120 grains.

RHUBARB

This contains considerable tannic acid as well as cathartic principles. The astringent action predominates with smaller doses (0.05 to 0.3 Gm.), which are used as astringent bitters in gastric catarrh, and in diarrhea. Larger doses (1 to 5 Gm.) are laxative with little colic. They may be employed in chronic constipation, but the astringent action makes it inferior to cascara. It may cause skin eruptions.

The cathartic principles are mainly a *resin*, non-glucosidal, but yielding on hydrolysis various anthraquinone derivatives, which also exist partly free: rhein, emodin, aloe-emodin, chrysophanic acid, etc. The astringent principles are glucosidal compounds of tannin (rheotannic acid), and gallic acid. There is also a large amount of calcium oxalate (Tutin and Clewer, 1911).

Preparations.—*Rhubarb*, U.S.P. (Rheum), the dried rhizome and roots of species of Rheum growing in China and Tibet (species cultivated in this country are devoid of cathartic principles), has been used since antiquity in China, and by the Roman physicians. ***Aromatic Rhubarb Syrup**, U.S.P. (Syr. Rhei Arom.), contains 15 per cent of the Arom. Tr. of Rhubarb, 0.1 per cent of pot. carbonate; dose, 10 cc., 2½ drachms. The *Aromatic Rhubarb Tincture*, U.S.P., contains 20 per cent of rhubarb with aromatics (cinnamon, clove and nutmeg); dose, 4 cc., 1 drachm.

ALOE

The dried juice of the leaves of various species of Aloe from the West Indies, Africa, etc., furnishes the commercial varieties of aloes, which differ somewhat in composition and action. They contain anthraquinone derivatives, especially aloins (10 to 16 per cent). These are glucosides which are probably inactive themselves, but which yield emodin and other active anthraquinone derivatives on cleavage. This cleavage occurs in the intestine; it is favored by alkalis and perhaps also by bile and by iron salts. Aloin may be used as such. Aloe is intensely bitter, so that it is administered in pills. Very small doses may be used as stomachic. Moderate doses are laxative, but somewhat likely to gripe, and are therefore commonly combined with belladonna or carminatives (myrrh, etc.). They do not lose their efficiency on continued use and would be suited to habitual constipation, but have no advantage over cascara. Aloes are supposed to produce considerable congestion of the pelvic organs and are therefore contraindicated in hemorrhoids, menstruation and pregnancy. On the other hand, they may be used as emmenagogues. They are especially prescribed for correcting the constipative action of iron medication. Neither aloe nor podophyllum is cholagogue or choloretic. They do not increase the output of cholic acid, cholesterol or bile pigments (Ivy, Annegers and Atkinson, 1942), nor do they stimulate the contraction or evacuation of the gallbladder (Ivy, Robuck and Stein, 1942); nor the flow of bile in constipated patients (Ivy, Roth and Gutman, 1945).

Aloin is also effective *subcutaneously*, being excreted into the large intestine, but this method is too painful (H. Meyer, 1890).

Aloin Nephritis.—In rabbits, hypodermic injection (2 cc. per kilogram of 5 per cent, repeated on two to three successive days) produces a tubular nephritis. The anatomic lesions have been investigated especially by Mürset (1885); they are practically the same in acute and chronic poisoning, and consist mainly in degeneration of the epithelium of the convoluted tubules. This loses its striations and staining qualities, and the nuclei disappear. The glomerular epithelium is but slightly altered, and the glomerular vessels show no lesions. The urine may be increased or diminished and contains proteins, leukocytes, casts, crystals and blood.

Metabolism.—There is also an increased protein metabolism, resulting in rise of urea in mammals, of uric acid in birds. The latter may develop gout. Dogs show some fever (Berrar, 1913).

Preparations.—***Aloe**, U.S.P., is the dried juice of the leaves of Aloe Perryi (Socotrine) or of A. vera (Curaçao). Brown, opaque glassy masses, aromatic odor, nauseous bitter taste; partly sol. in water, completely sol. in alc. Aloe was used by the Greeks and probably by the Egyptians. Dose, 0.25 Gm., 4 grains, best as pills. *Aloe Pills*, U.S.P., contain, each, 0.13 Gm., 2 grains, of aloes, with soap.

***Aloin**, U.S.P., a mixture of pentosides obtained from aloes (usually from Curaçao, W. Hills, 1908), varies in chemical composition, physical and chemical properties, according to the source. A yellow micro-crystalline powder, practically odorless, intensely bitter taste. Sol in water and alc. Dose, 0.015 Gm., ¼ grain. *Pills of Aloin, Strychnine, Belladonna and Ipecac*, N.F. (formerly "Compound Laxative Pills"), contain, each, aloin 16 mg. (¼ grain), strychnine 1 mg. (1/64 grain), ext. belladonna 8 mg. (⅛ grain), and ipecac 4 mg. (1/16 grain). They have caused many accidental deaths in children. *Nataloin* differs from the other aloins in composition, and is more difficultly hydrolyzed (H. Meyer). *Synthetic anthracene derivatives* with laxative action have been prepared, but have little practical importance (*purgatin*, anthrapurpurin diacetate; *exodin*, methyl esters of diacetyl-hexaoxy-anthraquinone).

PHENOLPHTHALEIN

This is a mild tasteless purgative, acting chiefly on the large intestine, similarly to the emodin cathartics. It is insoluble in water, but forms soluble salts with alkalis. Its action therefore depends on the alkalinity of the intestines and varies with this, so that the response is sometimes slight and sometimes excessive. It is but little absorbed from the alimentary canal, and is ordinarily nontoxic even in large doses; but even the ordinary dose may sometimes cause serious effects. It is used in habitual constipation, and has been exploited under several proprietary names (purgen, laxans, etc.). Phenolphthalein may be taken in the evening, as powder, capsules or lozenges, in doses of 0.1 to 0.2 Gm., 1½ to 3 grains; for bedridden patients, 0.5 Gm., 8 grains; for children, 0.03 Gm., ½ grain. These smaller doses soften and regulate the stools for several days, with little or no colic. Large doses are hydragogue.

Phenoltetrachlorphthalein, 0.4 Gm. dissolved in 20 cc. of neutral olive oil, has been suggested as a subcutaneous purgative (Abel and Rowntree, 1909; Rowntree, 1910).

For the diagnostic phenolphthalein derivatives, see Index.

Absorption, Fate and Excretion.—Phenolphthalein is insoluble in acids, but gives a pink solution with alkalis. It passes the stomach unchanged. It is partially dissolved in the alkaline intestine, but little is absorbed, almost the entire quantity (over 85 per cent) appearing unchanged in the feces (Vamossy). After large doses, traces are found in the urine (Elmer, 1909), which is then colored violet-red by alkalis (Gruebler, 1906). With the usual medicinal doses, it is present in the urine only in conjugation with sulfates; with large doses, a part may be unconjugated. The total urinary excretion is 1.4 to 20 per cent of the amount administered orally (Fantus and Dyniewicz, 1938). *After hypodermic administration*, it is excreted by the urine, feces, saliva, tears, etc. The excretion is rapid, beginning within fifteen minutes and ending in twelve to eighteen hours. The body fluids dissolve it more readily than water (Fleig, 1908). It is excreted into the intestine mainly by the bile and is to some extent reabsorbed in the large intestine (Abel and Rowntree .1909).

The purgative action of this familiar indicator was discovered by v. Vamossy, 1900, when investigating whether the substance would be harmless for denaturing artificial wines; it appears to be connected with the quinone structure. It is but slightly cathartic in rats, cats and dogs, but is effective in rhesus monkeys, although the response is variable. "Yellow phenolphthalein" contains some impurity which renders it about three times as potent as white (E. F. Williams *et al.*, 1934). Ott and Scott, 1908, found evidence that phenolphthalein acts directly on the muscle of the excised intestine. Fleig and others attribute the action to increased intestinal secretion, but the evidence is not satisfactory. It acts also on hypodermic or intravenous administration, reaching the intestine through the bile. *Bile* appears to be necessary for its action, for it is ineffective in obstructive jaundice (T. Steigmann *et al.*, 1938). The blood pressure is scarcely affected, even when large doses are injected into a vein; the kidneys are not irritated, nor are there any other systemic effects. Phenolphthalein itself does not produce local irritation, but its soluble salts are highly irritant. It is not bactericidal (Abel and Rowntree).

Toxic effects in the use of phenolphthalein are exceptional, but may be serious. They consist in enteritis, especially colitis; dermatitis; and hemorrhagic tendencies. One death has been reported (M. Cleeves, 1932). On the other hand, large doses have often been given without bad effects; to man, several grams by mouth, 0.5 Gm. subcutaneously; to dogs, 1.25 Gm. per kilogram. Activated charcoal has been recommended as antidote (Fantus and Dyniewicz, 1938).

Cases of clinical toxicity were reported by Orland, 1913, and others. They presented phenomena of intestinal irritation, ending in recovery. *Dermatitis* was reported by Wise and Abramowitz, 1922, and C. F. McCarthy, 1932. It occurs only in susceptible persons, and consists in erythematous and vesicular rashes of various types, similar to those of antipyrine and arsphenamine. They may be followed by persistent pigmentation. Rosenbloom reported nasal *herpes*. Medicinal doses do not produce *albuminuria* (Fantus and Dyniewicz, 1937).

The sale of phenolphthalein in the United States decreased from 460,000 pounds in 1937 to 245,000 pounds in 1939. The fall may be placed to the credit of the regulations of the Food and Drugs Administration.

***Phenolphthalein**, U.S.P. (Dihydroxyphthalophenone), $(C_6H_4OH)_2CO.C_6H_4CO$, is a white crystalline powder, odorless and tasteless. Almost insol. in water, sol. in alc. (1:13). Dose, 0.03 to 0.12 Gm., ½ to 2 grains. McGuigan *et al.*, 1944, found 0.06 Gm. ineffective in over half the cases; normal individuals required about double, constipated about three times this dose. The same relation held for the official dose (1 Gm.) of cascara sagrada.

CASTOR OIL

This consists mainly of the triglyceride of an unsaturated fatty acid, ricinoleic acid. The neutral fat is not active, but becomes so when it is saponified in the intestine. The cathartic effect is due mainly to motor stimulation of the small intestine. The fluid character of the stools is due to the quicker passage of the feces; the intestinal secretion is not increased.

With the usual dose, ½ to 1 ounce, the response is certain and complete, resulting in a few hours in one or two extensive semifluid stools, with but slight hyperemia or irritation, and little or no colic. The evacuation is so complete that there may be some after-constipation. It is especially suited to the treatment of acute constipation or acute diarrhea from dietetic errors, ptomaine and other poisoning, etc. Continued use may produce gastric disturbance. There is some pelvic congestion, so that it is avoided during menstruation and pregnancy.

Mechanism of action was studied with x-ray by Magnus, 1908, and his observations have been confirmed on man. The pure oil delays slightly the passage through the *stomach* (as do other neutral oils). Rancid oil hastens the gastric expulsion. In the *small intestine*, the segmenting movements and peristalsis are greatly increased, so that the expulsion may be completed in two hours instead of the normal eight hours. In the *colon*, the normal antiperistalsis is allayed, so that the feces escape concentration. The propulsive movements of the colon are not much increased, but the passage of the fecal material is hastened by its thinner consistency. In China it is used as an article of diet. The properties of castor oil were known to Herodotus; but croton seeds were first described in the middle of the sixteenth century. A small amount, 1 to 2 per cent, of castor oil is added to alcoholic *scalp lotions* to leave a slight oil film on the hair. Castor oil is said to be an active *poison for flies* (Boyes and Gurjot, 1919).

Administration.—It is best given an hour before breakfast. The taste may be somewhat disguised by wetting the mouth with hot coffee or milk, and giving the well cooled oil floating in these liquids, so that it will not be so adherent. The aftertaste may be mitigated by peppermint or bread. The *soft gelatin capsules* are tasteless, but since the ordinary size contains only 1 cc., it is difficult to administer an effective dose.

***Castor Oil**, U.S.P. (Oleum Ricini), is a fixed oil expressed from the seed of Ricinus communis. An almost colorless viscid oil, of faint but characteristic odor and extremely disagreeable taste. Sol. in an equal volume of alc. Dose, 4 to 16 cc., 1 to 4 drachms; for infants, a teaspoonful. *Aromatic Castor Oil*, N.F., contains aromatic flavor and saccharin.

RICIN

Occurrence, Clinical Symptoms and Treatment.—This toxic protein is contained in the castor seeds, but does not pass into the oil. Similar phytotoxins occur in croton seeds (*crotin*), and in jequirity seeds (abrin); in the bark of the locust tree, Robinia pseudoacacia (*robin*); and in the seeds of some leguminous plants (*phasin*). The last is but weakly toxic. The ricin is responsible for the toxic effects on eating the castor seeds; five or six of these are fatal to a child, twenty to adults; three or four seeds may cause violent gastro-enteritis, with nausea, headache, persistent vomiting, colic, sometimes bloody diarrhea, thirst, emaciation and great debility. The symptoms usually do not set in until after several days. More severe intoxications cause small frequent pulse, cold sweat, icterus and convulsions. Death occurs in six to eight days, from the convulsions or from exhaustion. The fatality is about 6 per cent. This low fatality is due to the destruction of the poison in the alimentary canal. The *treatment* would be evacuant and symptomatic. Three to ten days are required to complete recovery (critical review and bibliography, Ford, 1913).

Effects on Animals.—The actions can be best studied on rabbits, by hypodermic or intravenous injections. Even with the latter there is an incubation period of at least twelve to eighteen hours before symptoms appear. These correspond to those described for man. They are partly local—gastro-enteritis; and partly central—paralysis of the respiratory and vasomotor centers. Local inflammation also occurs on other mucous membranes to which the poison may be applied, especially the conjunctiva. The phytotoxins have no direct effect on muscle or nerve.

The *autopsy* findings consist in characteristic swelling and reddening of Peyer's patches and mesenteric lymph glands, internal hemorrhages and diffuse nephritis. Flexner, Mueller and others showed that these lesions are not due to thrombosis, but to direct action on the tissues. The site of the injection is boggy. *Temperature* greatly affects the action of ricin. Frogs at 4° C. are not killed by more than a thousand times the dose that is fatal at 37° C. Conversely, hemagglutination requires 100 to 1000 times the concentration at 38° than at 4° C. (Moriyama, 1934).

Action on Blood.—*In vitro*, ricin hemolyzes and agglutinates the corpuscles of nearly all warm-blooded animals (Stillmark, 1888). The agglutination does not seem to occur in the body. Leukocytes, epithelial and other cells (except those with thick membranes, as yeast) are also agglutinated; as likewise the stroma of laked corpuscles (Elfstrand). The presence of serum hinders the effect. The agglutination has been referred to precipitation of the nucleo-albumins (Stassano) or other proteins, such as those of serum (Kraus, 1902). All kinds of colloid precipitates carry down ricin, which is adsorbed by solid proteins and lipoids.

Nature of Ricin.—This appears to be a true protein, for a preparation of ricin has been obtained which is a typical albumin and is so active that 0.0005 mg. is fatal to a kilogram of rabbit (Osborne, 1909). The agglutinating action is also powerful.

Antiricin.—Injections of the phytotoxins produce typical antitoxins, so that an immunized animal can survive 5000 ordinary fatal doses of ricin. Some of the basic work of Ehrlich was done with ricin and abrin. He showed (1891) that the immunity starts in five to six days, and lasts six or seven months. The resistance of the corpuscles is unchanged, the antiricin being contained in the pseudoglobulin fraction of the serum (Jacoby, 1902). It contains antitoxin, antiagglutinin (probably identical) and precipitin. Madsac and Walbum found that this combination obeys the same laws as diphtheria antitoxin. The toxicity of ricin is modified rather complexly by lecithin (Lawrow, 1913).

ABRIN

Abrin, from *jequirity beans* (Abrus precatorius), closely resembles ricin in action, but immunity against one does not protect against the other (Hausmann, 1902). The literature was reviewed by Ford, 1913. Abrin is n-methyltryptophane. Various derivatives have been synthetized and compared by Cahill and Jackson, 1938.

Poisoning.—When the whole beans are swallowed, no toxic effects result, since the shell is so hard that the poison does not dissolve. But if the powder is taken, it produces effects similar to those of ricin. Its toxicity is greatly increased by heating the animals (Lesne and Dreyfus, 1913).

Use in Ophthalmology.—The action on the eye is much stronger than with ricin, producing ophthalmitis. It has been used therapeutically (Weeker, 1882) to clear corneal opacities. This is dangerous unless standardized preparations are used and excessive effects are checked by an antiserum.

CROTON OIL

This contains, besides ordinary fats, about 10 per cent of "croton-resin," the active component (Dunstan and Boole, 1895), producing the local and systemic effects of the oil (Kobert and Hirscheydt, 1890; Boehm, 1915). Croton oil is the most violent of all cathartics, ½ to 1 drop producing burning in the mouth and stomach, often vomiting, and after one-half to three hours, several extensive fluid evacuations, with much colic and tenesmus. It was formerly used in extreme cases of constipation (lead), and in unconscious patients (uremic and apoplectic coma), but it should never be employed. It may produce severe local effects on the mouth, as well as gastro-enteritis. Toxic doses cause collapse. Twenty drops have been fatal, but recovery is said to have followed ½ ounce—presumably because of vomiting. The *treatment* would be evacuant, demulcent, opiates and symptomatic (directed against the enteritis and collapse).

Applied externally, croton oil produces irritation, proceeding to pustulation and even sloughing. When diluted with 2 to 10 parts of olive oil, it may be used as counterirritant, but is dangerous.

Croton Oil (Oleum Tiglii), N.F., is a fixed oil expressed from the seeds of Croton Tiglium. A pale yellow or brownish-yellow, somewhat viscid and slightly fluorescent liquid, having a slight fatty odor. Slightly sol. in alc. Dose, 0.06 cc., 1 minim, on a lump of sugar, slice of bread or lemon.

CATHARTIC RESINS

Jalap, Colocynth, Podophyllum, Elaterin and similar drugs contain active principles which are for the most part resinous (*i. e.*, soluble in alcohol, but slightly soluble in water), often glucosides. On chemic manipulation (probably hydration) these yield resinous acids which are much less active. The resins are highly irritant, producing considerable colic (sometimes vomiting), and several watery stools; in one or two hours with jalap and most of the others, but with podophyllum only after twelve to twenty-four hours. They are used especially in dropsies (Compound Jalap Powder); small doses of podophyllum also as laxative in habitual constipation. The others tend ultimately to produce constipation. Colocynth, and presumably the others, stimulate peristalsis in the small intestine, inhibit antiperistalsis in the colon, and lead to the effusion of fluid from the whole intestinal canal. The resins require the presence of *bile,* which renders them soluble. They are therefore less active in obstructive jaundice. They produce griping and are often prescribed with belladonna and aromatics. If they are not removed by catharsis, they may cause severe enteritis.

The principles are *not as effective when given pure* as when they are mixed with extractive, as in the crude drugs and "resins" (alcoholic extracts precipitated by water), or as preparations of the crude drug. This is due, in some cases, to their being somewhat soluble, and therefore absorbed in the stomach.

Subcutaneous administration produces diarrhea with podophyllin and colocynthin, but is not employed because it also produces nephritis, local irritation and abscesses.

The mechanism of action was studied on colocynth by the x-ray method by Padtberg, 1909. Similar observations have been made with jalap on man: the gastric movements may be slightly increased, but often remain normal. In the *small intestine* the peristalsis is so much quickened that the contents may be completely expelled in half an hour instead of the normal eight hours. This is accomplished by the effusion of considerable fluid into the lumen. In the *large intestine* the propulsion is only slightly increased; but the stools are rendered still more liquid by the inhibition of antiperistalsis and by the secretion of additional mucus. Padtberg, 1911, found that the colocynth peristalsis and effusion are arrested by morphine and opium, although these do not ordinarily act directly on the intestine, but on the stomach.

Unanesthetized dogs with Vella fistulas respond to *intravenous injection* of colocynth or podophyllin as to instillation into the lumen, by strong peristaltic waves while the general tonus of the intestines is decreased (Gruber, Richardson and Bryan, 1932). *Excised segments* of small intestines of rabbits show increased tonus and diminished amplitude. With gamboge, tonus and amplitude are both decreased (N. Hollander, 1927, 1935).

Other Actions.—Excised *uterus* reacts similarly to the intestines. The *frog heart* responds to moderate concentrations by increase of amplitude and of tonus, and finally by systolic arrest. The response to *parasympathetic* stimulation is paralyzed in the intestines, heart and uterus (Hollander, 1935). Convolvulin and jalapin appear related to saponin and agaricin. They are hemolytic in neutral solution. This has been suggested as an index of the intestinal action, but the relation requires confirmation (G. Heinrich, 1918). They are destroyed by alkalis, not by acids.

RESIN OF PODOPHYLLUM

This acts slowly, generally only after twelve to twenty-four hours or longer, producing several soft stools. Larger doses (20 mg., $\frac{1}{3}$ grain or more) act as a hydragogue cathartic; but it is chiefly employed in small doses (5 to 10 mg., $\frac{1}{10}$ to $\frac{1}{6}$ grain) as a laxative in chronic constipation; often combined with aloes or calomel, 0.3 to 0.5 Gm. has been fatal. It is neither chologogue nor choleretic (see Aloe).

Podophyllum Resin, U.S.P. (Podophyllin), is prepared from the dried rhizome and roots of Podophyllum peltatum (May Apple, Mandrake), a plant used by the Indians. An amorphous greenish-yellow powder, of slight peculiar odor and faintly bitter taste. Sol. in alc., insol. in water. Active constituents, resin and a crystalline principle, podophyllotoxin. Dose of the resin, 0.01 to 0.065 Gm., $\frac{1}{6}$ to 1 grain. Very irritating to mucous membranes, esp. of the eyes. Local application of a 25 per cent suspension in liquid petrolatum removes *condyloma acuminatum,* granuloma inguinale and excessive granulations of surgical wounds. The growths blanch within a few hours, become necrotic in one or two days, and drop off on the second or third day, without ulceration or gross scarring. Recurrences are few and can be treated in the same manner. The surrounding normal tissue is usually not affected, nor are true warts nor benign rectal polypi. There are no systemic reactions (Culp and Kaplan, 1944; Tomsky *et al.,* 1942). A single application of podophyllin to *normal* skin, human or rabbit's, produces a transitory alteration in the nuclear pattern of the epidermis, lasting four to six days (J. S. King and Sullivan, 1946).

Other roots and rhizomes related to this group include *Leptandra* (Culver's Root), from Veronica virginica. Contains an amorphous bitter principle, and not a crystalline glucoside, as formerly reported (Power and Rogerson, 1910). "Leptandrin" is a resinoid. Pharmacologically inert, but was supposed to be cholagogic without producing intestinal irritation. Dose, 1 Gm., 15 grains. *Stillingia* (Queen's Root), from Stillingia sylvatica, contains pungent resin and volatile oil. Used mainly in domestic medicine in purgative mixtures, and also as nauseant and emetic. Dose, 2 Gm., 30 grains. *Juglans* (Butternut) is the root bark of Juglans cinerea, collected in autumn. Used as rather mild laxative. Dose of extract, 1 to 2 Gm., 15 to 30 grains. The fldext. of the root, 5 to 20 minims, is said to be a gentle and prolonged laxative similar to rhubarb, and was used in chronic constipation. *Iris* (Blue Flag), from Iris versicolor. Power and Salway, 1911, could not find any active principle, although the drug and the resinoid "iridin" were formerly considered cathartic and diuretic. Dose, 1 Gm., 15 grains. *"Orris Root"* (Iridis Rhizoma), from several cultivated species of iris. Has a violet odor. Is used in sachets and tooth powders, but allergic reactions are rather frequent.

JALAP, SCAMMONIUM, IPOMEA

Jalap is perhaps the mildest member of the group. It produces watery stools within three or four hours, with little intestinal irritation, without gastric disturbance or much prostration. It has little taste and is easily administered. It is used in ascites, cerebral congestion, hypertension; and as adjuvant to anthelmintics. *Scammony* and its equivalent *Ipomea* are closely related to jalap.

Jalap, N.F., is the dried tuberous root of Exogonium Jalapa (Ipomoea purga). Dose, 0.3 to 1.2 Gm., 5 to 20 grains. The constituents have been studied by Power and Rogerson, 1909 and 1912. The *"resin"* is a complex substance, which can be separated by solvents into several glucosidal portions: Jalapin (convolvulin, jalapurgin) and Scammonin (orizabin). *Compound Jalap Powder,* N.F., consists of jalap, 35 per cent, and pot. bitartrate, 65 per cent. Dose, 0.6 to 4 Gm., 10 to 60 grains. *Ipomoea* (Orizaba Jalap, Mexican Scammony) is the dried root of Ipomoea orizabensis. Dose, 0.3 to 1.2 Gm., 5 to 20 grains. *Scammony* is the dried root of Convolvulus Scammonia. It was used by the ancients The dose of *Scammony Resin* is 0.03 to 0.2 Gm., $\frac{1}{2}$ to 3 grains.

COLOCYNTH, ELATERIN AND BRYONIA

A number of plants of the cucumber family yield these drastic drugs. They are of complex composition, each containing several active principles, resinous and alkaloidal. They produce continuous watery stools, with intense irritation and hyperemia. They were formerly employed to reinforce the action of other purgatives, as in the "Compound Cathartic Pills." Colocynth is excreted by the kidneys and milk, and should not be used by nursing women. Elaterin is one of the most powerful cathartics, but is too irritant and causes dangerous prostration.

Bryonia, the root of Bryonia alba and dioica, was used in homeopathy against pneumonia. It was recommended by the "Women Physicians of the Salerno School," about 1100, to redden the face. The introduction of Bryonia into the pleural cavity of animals is said to produce fibrous effusion. According to Jensen, 1915, the fresh root is much more poisonous than the dried. The toxic principles are more abundant in the autumn. At that time the root contains two glucosides: bryonin, soluble in water, inactive; and bryonidin, insoluble in water, paralyzing the nervous system on peritoneal injection. Power, 1912, considers bryonin and bryonidin as impure mixtures and attributes the purgative action to non-glucosidal resins and alkaloids. The dose of Bryonia is from 0.6 to 4.0 Gm., 10 to 60 grains.

Colocynth (Bitter Apple) is the dried pulp of the unripe but full grown fruit of Citrullus Colocynthis. Dose, 0.12 to 0.3 Gm., 2 to 5 grains; 0.6 to 1 Gm. is seriously toxic; 4 Gm. may be fatal. It was one of the constituents of the obsolete "Compound Cathartic Pills" (Comp. Pills of Mercurous Chloride, N.F.). *Gamboge* (Cambogia) is the gum resin from Garcinia Hanburyi. The resin (70 to 80 per cent) contains garanolic acids, which form readily soluble compounds with alkalis, and thus become active in the intestine. The effects resemble those of colocynth; 4 Gm. are fatal. Rarely used in pills. Dose, 0.125 Gm., 2 grains.

Elaterin is a neutral principle obtained from the juice of the fruit of Ecballium Elaterium (used in antiquity). Elaterin consists of two crystalline substances, the levorotatory α-elaterin, which is inert; and 60 to 80 per cent of the active dextrorotatory β-elaterin. Commercial elaterin varies in composition and activity (Power, 1912). Elaterin does not exist as such in the fruit, but is formed during the expression by a diastatic ferment, acting on a glucoside (Berg, 1909). Insol. in water, slightly sol. in alc. (1:325). Dose, 3 to 6 mg., $\frac{1}{20}$ to $\frac{1}{10}$ grain, repeated in five hours if necessary, but not daily; 0.6 Gm. may be fatal. The dose of *elaterium* is 6 to 30 mg., $\frac{1}{10}$ to $\frac{1}{2}$ grain.

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CHOLAGOGUES AND CHOLERETICS

The term *cholagogue*, formerly applied to all agents that increase bile flow, is now restricted to those that stimulate evacuation of the gallbladder. Those that increase the actual secretion of bile are termed *choleretics* (Brugsch and Horsters). Significant increase of bile formation is produced by administration of the bile salts and their close derivatives. Salicylate, cinchophen, benzoate and sodium oleate cause some increase; water increases the volume, but not materially the solids. These are practically the only choleretics. The increases reported for other drugs are generally due, not to increased secretion of bile, but to evacuation. The principal cholagogues in this sense are fatty foods; a hormone, "cholecystokinin," produced by them; and (rather weakly) the parasympathetic stimulants (review, A. C. Ivy, 1934). The stools, with moderate *catharsis*, have usually a darker color, suggesting an increased bile content. This is not due to increased secretion of bile, but to the more rapid passage of the intestines, leaving less time for reabsorption and decomposition. The dark color of calomel stools is due chiefly to the oxidation of the bile pigment to a greenish color.

Function of the Gallbladder.—This viscus is not essential, for it is not present in all animals. It is found in most vertebrates, including the mouse, but not in the rat or horse. With the pigeon, it exists in the embryo and disappears later. In man and the animals that have a gallbladder, the bile flows continuously into this reservoir from the liver and is discharged drop by drop into the duodenum during digestion. The slow discharge is advantageous for the emulsification of oil, by securing better contact. The arrival of the bile in the intestines is also a "primer" for increasing the direct secretion of bile, by the absorption of the bile acids. During its sojourn in the gallbladder the bile is concentrated to $\frac{1}{4}$ to $\frac{1}{10}$ of its volume by the absorption of water, together with sufficient inorganic salts to keep it isotonic. This increases the colloids and viscosity to that of a fairly thick mucilage which assists in emulsification. The bile acids, pigments and cholesterol are absorbed slightly.

Evacuation of Gallbladder.—Klee and Klüpfel, 1914, found that this is stimulated by eating, entrance of the chyme into the intestine, injection of Witte's peptone, and especially by the administration of olive oil. No effect was produced by soap and hydrochloric acid. The rhythmic movements are increased during digestion, or by the introduction of acid into the duodenum (Toyoshima and Tsurmaki, 1927). Clinical roentgen observations show that *meals*, especially with fat (cream or egg yolk), evoke gradual contraction and discharge of the gallbladder, beginning when the food passes from the stomach into the duodenum, and generally ending in half an hour, when the gallbladder is about three-fourths emptied (E. A. Boyden, 1927). Similar phenomena have been observed in the flow from the papilla of Vater transplanted into the skin (Winogradow, 1927). The stimulating effect of fats on the gallbladder is not direct, for it is not produced by intravenous injection of emulsified fat or fatty acids or extracts of egg yolk (review, Ivy, 1934).

Cholecystokinin, which exists in acid extracts of the duodenal mucosa, is a potent stimulant of the gallbladder. Intravenous injections of purified fractions raise the gallbladder pressure and secure evacuation, in man as well as in animals. It is probably related to secretin, but they are not identical (review, Ivy, 1934).

Autonomic Drugs on Gallbladder Movements.—The vagus innervation is predominantly motor, the sympathetic inhibitory (Lieb and McWhorter, 1915). Contraction of the gallbladder results in rise of pressure, but not necessarily in evacuation, for the latter requires coordination with the Oddi sphincter.

Parasympathetic Drugs: Pilocarpine, physostigmine, choline and acetylcholine produce marked contraction, but evacuation does not usually result from therapeutic doses in man. Atropine tends to relax the tonus, and therefore permits better filling and tends to delay evacuation. *Sympathetic Stimulants:* Epinephrine and ephedrine have little effect on intravenous injection; they are somewhat depressant to excised preparations. *Muscular Stimulants:* Cholecystokinin contracts and evacuates effectively. With *pituitrin*, hypodermic therapeutic doses in man tend to evacuate, but are less effective than olive oil. The tonus response is variable. *Histamine* increases the intravesical pressure in situ, chiefly by increase in the liver volume. It causes marked contraction in the excised bladder. *Barium* causes contraction. *Guanidine* has little effect. *Muscular Depressants:* Magnesium intravenously, nitrite, ether and alcohol relax the tonus, but have little effect on evacuation. *Miscellaneous: Nicotine* is slightly evacuant in cats; it tends to relax the tonus in situ, and to increase it in the excised. *Ergotamine* produces slight increase of tonus. *Morphine* has little effect, but tends to relax the tonus and increase the amplitude of the rhythmic contraction. *Papaverine*, *sodium salicylate, peptone* and *calomel* have little effect (Lieb and McWhorter, 1915; M. L. Voegtlin and Ivy, 1934, dog in situ; G. M. Higgins *et al.*, 1935, excised; review, Ivy, 1934).

Sphincter of Biliary Papilla.—Reach, 1914, reports that the tonus is increased and the bile flow correspondingly hindered, by morphine, epinephrine, pilocarpine and atropine.

The duodenal-bile reflex to magnesium sulfate is discussed under that drug (see Index).

Choleretic Agents.—The *bile acids* are the most effective substances for increasing the secretion of bile. *Cinchophen* ranks high. It increases the volume up to five times the normal, persisting for four to five hours, with nearly normal concentration of the bile pigments, so that their output is materially increased. The bile salts and cholesterol are decreased. *Salicylates* (5 Gm. per day), benzoates and intravenous injection of phenolphthalein derivatives also cause considerable increase of bile secretion.

The choleretic effect of bile administration was demonstrated by Schiff, 1870. As regards less potent agents, the older experiments on animals with biliary fistulas gave contradictory results because they did not extend over sufficient time to discount the natural variations in bile flow. Reliable experiments on a human patient were made by Pfaff and Balch, 1897. Soto, 1929, working on dogs with aseptic biliary fistulas and fairly constant twenty-four-hour bile secretion, confirmed the choleretic action of salicylate, benzoate and a few others, and the inefficiency of cathartics (calomel, aloes, cascara, phenolphthalein), of sodium sulfate, citrate and acetate, and of methenamine. Chabrol and Maximin, 1929, obtained positive results with bile salts, cinchophen, salicylate and saline cathartics; no increase with acetylsalicylic acid, glycerol, acetyl choline, posterior pituitary and magnesium sulfate. Chabrol, Charonnat *et al.*, 1931, tried some fifty aliphatic substances on biliary fistula dogs, and found only three choleretic (sodium oleate, chloralose and sodium monochloracetate). W. B. Bradley, 1938, studied the response to cinchophen and dehydrocholic acid on biliary fistula dogs.—*Turmeric,* the rhizome of *Curcuma magna,* commonly used in cookery to give a yellow color to relishes, is said to cause marked choleresis by irritation of the hepatic cells; large doses cause fatty degeneration of the liver. It also stimulates the gallbladder. Its action is attributed to a terpene, "curcumene" (Guttenberg, 1927; Kalk and Nissen, 1931).

BILE

The administration of bile or bile salts (sodium glycocholate and taurocholate) stimulates the secretion of bile (Pfaff and Balch, 1897), increases peristalsis (Stadelmann, 1896), and intestinal propulsion (bolus-method, Haney *et al.*, 1939); acts as an indirect antiseptic (Limbourg) by evacuating the intestines; and facilitates the digestion of fat and the solution and absorption of liposoluble substances, such as carotene and K vitamin. They also aid in the absorption of iron. The normal output is fully adequate for these functions, but their administration is indicated whenever the bile fails to reach the intestines after operations on the biliary system. Their use in obstructive jaundice may be limited by the retention symptoms. Added to enemas, bile is used as a laxative against impacted feces and against ascaris, but has little advantage over soap.

The *pharmacologic actions* of bile salts are similar to those of saponins. Like these, they lower surface tension, hemolyze blood, irritate mucous membranes and have a digitalis-like action on the heart. Injection of bile into the intestines does not increase the secretion of pancreatic juice, but weakens the secretory response to injection of peptone, soap and acid (J. E. Thomas and Crider, 1943). Bile is nontoxic by mouth, but when injected into the circulation (Bunting and Brown, 1911) it produces severe nervous and cardiac depression and hemolysis. It is also directly toxic to muscle and nerve. These effects are due to the bile acids. These act as "*hydrotropic*" agents, conferring water solubility on fatty acids, cholesterol, resins, calcium carbonate, phosphate, and the like. The pigments have no marked effect on the circulation or respiration, even on intravenous injection (W. C. Emerson, 1929).

Toxic symptoms of biliary retention (obstruction) consist in dulness, delirium, convulsions, fever, generally fatal in a few days. It is not certain that these effects are due entirely to bile acids or pigments.

The *chemical structure of cholic acid* is related to that of cholesterol, differing chiefly in the side chains. It seems to be formed exclusively in the liver, and bile salts are decreased or abolished by hepatoxic poisons, chloroform or carbon tetrachloride (Bollmann and Mann, 1936). It exists in the bile solely as conjugated compounds with amino acids, glycocholic acid with glycine, and taurocholic acid with taurine, the latter being less toxic. If free cholic acid is administered, it is conjugated so far as glycine, taurine and time are available (Josephson *et al.*, 1938). *Endogenous bile acid production* depends largely on diet. It is high with meats, especially those rich in tryptophane and proline; carbohydrates decrease it; cholesterol has no effect (Foster, Hooper and Whipple, 1941). Numerous derivatives have been prepared synthetically. Cholic acid is also related to bufotalin (toal poison); saponins have a similar structure.

Fate.—Bile salts are *absorbed* promptly and almost completely from the intestines (A. L. Berman *et al.*, 1940), carried to the liver by the portal blood, and again reexcreted into the bile. Only a small part is lost in this cycle (Hoppe-Seyler, 1863), and correspondingly little is synthesized. If bile salts are injected into a vein they are promptly absorbed by the vascular endothelium and then enter the cycle. Very little goes into the urine (review, B. Josephson, 1941). The daily output of cholic acid from biliary fistulas in man ranges from 1 to 2.3 Gm. If the bile is refed, the daily output is about four times this figure (Josephson and Larsson). Treatment with thyroxin interferes with biliary secretion (L. H. Schmidt, 1937).

Choleretic Action.—Intravenous injection of bile salts increases the rate of bile flow to double or more. The action begins in about fifteen minutes and lasts one to two hours. The total output of bile acids, pigment and cholesterol is also increased, although their concentration in the bile may be diminished. This is followed by a compensatory decrease as their level in the serum falls. The total excretion of bile salts falls somewhat below the amount administered (H. A. McGuigan, 1944). The same changes can be produced clinically by oral administration of bile salts or bile. Conjugated bile acids are more effective than cholic acid, and are surpassed by some of the derivatives; for instance, dehydrocholic acid and deoxycholic acid (Hooper and Whipple, 1917; Doubilet, 1937).

Intestinal Absorption.—*Oleic acid,* which is practically unabsorbable from intestinal loops in the absence of bile, is absorbed when bile salts are introduced, practically parallel to their concentration (Verzár and Laszt, 1934; Riegel *et al.*, 1935). In buffer mixtures of *p*H above 6.25, oleic acid is completely dissolved by bile salts, ultramicroscopic observations and diffusion experiments indicating true molecular solution (Verzár and Kuthy, 1929; review, A. C. Frazer, 1940). Bile salts do not exert a hydrotropic action on neutral fats, but promote their emulsification. Lipase is activated partly at least by the emulsification of the fat. Liver esterase is inhibited. The favorable effects on the *absorption of the fat-soluble vitamins A, D and K,* of *carotene* and of *iron* are discussed under these substances (see Index).

The *hemorrhagic tendency* of the biliary deficiency of obstructive jaundice and of biliary fistulas is due to deficiency of prothrombin, which results from the failure to absorb K vitamin in the absence of bile acids. It is promptly corrected by the oral administration of bile acids together with K vitamin, as such or in the diet (Nygaard, 1932; A. J. Quick *et al.*, 1935; Hawkins *et al.*, 1938; E. D. Warner *et al.*, 1938). Hoessler and Stebbins, 1919, claimed that *direct addition of bile to blood* also delays clotting

Detoxifying Action of Bile.—Addition of acids to bile precipitates the bile acids, which then adsorb alkaloids, toxins and other substances (Clementi and Pistorio, 1929).

Bile Salts in Gonorrhea.—Loehlein, 1909, introduced the local injection of bile salts in the acute stage for destroying the gonococci. Hofmann, 1912, found that 1 to 2 per cent had little effect; 5 to 10 per cent gave better but only temporary results.

Toxicity.—Excessive concentrations of bile salts are highly toxic. Small doses stimulate the vagus center; larger doses depress the heart directly, with slow irregular pulse and low blood pressure. They also produce depression of the medullary centers, coma and paralysis; and hemolysis and cell destruction. They have a local vasoconstrictor action (Samelson). Eel serum poison, *ichthyotoxin,* appears to be related to the bile acids (F. Flury, 1929).

Neuromuscular Systems.—The bile salts were reported to act chiefly on the myoneural junction and on the reflex centers of the cord (F. A. Ries and Still, 1930). Bile and bile salts increase *peristalsis* clinically on oral administration or by enema (Glaessner and Singer, 1910). They increase markedly the propulsion of a bolus when introduced into a Vella loop of dog intestine. The other constituents of bile are not concerned in this (Haney *et al.*, 1939). On excised small or large intestines, bile or bile salts produce mainly depression (Ott and Scott, 1909; C. Schwarz and Magerl, 1924), but the large intestines may be stimulated (Schuepbach, 1910). Bile and bile salts, in moderate concentrations, increase the contractions of the pregnant, not of the virgin, uterus. High concentrations inhibit (Cantoni, 1914). Tommaselli, 1930, obtained complete paralysis even with 1:30,000 dilution of sodium cholate. *Excised frog hearts* are strengthened by low concentrations of bile salts. Moderate concentrations cause weakening and irregularity; higher concentrations produce systolic arrest (Shoda and Tominaga, 1927). Bile salts produce reversible contracture of *skeletal muscle. Motor nerve* is first stimulated then depressed by immersion in solution of fresh bile (Perichanjanz, 1921). Purified bile salts are only slightly toxic to muscle and nerve fibers (Ries and Still, 1930).

Cholic acid derivatives have been introduced for therapeutic use, especially for intravenous injection of the sodium salts, as being less toxic than and perhaps twice as potent as ordinary bile salts. For oral administration, however, Doubilet, 1937, found the natural conjugated cholic acid more effective than the desoxycholic, and this more than dehydrocholic acid.

Dehydrocholic acid, N.N.R. (decholin), an oxidation product of cholic acid, is used by mouth or intravenously to increase the volume of bile in the postoperative management of bile tract surgery; in functional insufficiency of the liver and to hasten the shadow of roentgenopaque substances in cholecystography. It does not stimulate gallbladder evacuation. It is contraindicated in complete biliary obstruction, and does not materially hasten the clearance of jaundice after a biliary obstruction is removed. It is claimed to have only a tenth of the *toxicity* of the taurocholate, intravenously (Gillert, 1928). Repeated injections of large doses cause diarrhea. *Renal lesions* with regressive and regenerative changes of the tubular epithelium have been reported in animals. They suggest caution in this therapeutic use (H. L. Stewart and Cantarow, 1935). It is reported to be *diuretic* in hepatic cirrhosis and to potentiate the clinical diuretic response to salyrgan (de Castro, 1934) and to mercupurin (Modell and Gold, 1944). The *choleretic action* amounts to about 40 per cent of the bile volume after intravenous injection of 2 Gm. of the sodium salt into patients (Rusznyak, 1927). In dogs, 5 mg. per Kg. by vein increases the flow to six and one-half times during the first hour (W. B. Bradley, 1938). The *hemolytic* action is only $\frac{1}{120}$ that of the tauro- or glycocholate *in vitro*, and is not attained clinically (E. E. Ziegler, 1931; E. Neubauer, 1921 to 1927). It has the *hydrotropic action* of bile salts and renders estrogens diffusible (Cantarow *et al.*, 1944). The oral dosage is 0.25 to 0.5 Gm. two or three times daily, after meals, for four to six weeks. It has a bitter taste. *Sodium dehydrocholate* is injected slowly by vein as 5 to 10 cc. of the 20 per cent solution, on three successive days. A *circulation-time test* involves perception of the bitter taste after injection of 3 cc.

Deoxycholic acid (*degalol*) was investigated especially by Heinrich Wieland, 1920, and J. Pohl, 1922. The choleretic response on intravenous injection is about double that of cholic acid. Wieland reported that it is twice as toxic; E. U. Still, 1929, claims that it is slightly less toxic. Its advantage appears doubtful (report, Council on Pharmacy and Chemistry, 1941, J.A.M.A., *117*:361).

Ketacholanic acid, a mixture of oxidation products of bile acids, is claimed to have a lower toxicity than the other derivatives, with about equal choleretic potency (C. F. G. Dolkart, 1937).

Bile Pigment.—In man this consists almost entirely of bilirubin; this may be oxidized to biliverdin, which is much more abundant in animals than in man. Bile pigment is formed from hemoglobin and myohemoglobin by the reticulo-endothelial cells generally, especially in the bone marrow, spleen and liver (Whipple and Hooper, 1913), but the role of the liver is chiefly that of excretion (Mann, 1927). Its formation continues after removal of the liver (F. C. Mann, Bollman and Magrath, 1924) and of all abdominal viscera (A. R. Rich, 1925). Its quantity depends on the rate of blood destruction. Bilirubin is chiefly responsible for the yellow color of normal blood serum, although carotenemia may play a part (E. F. Nation and Myers, 1934). The blood plasma normally contains 0.5 to 1.5 mg. of bilirubin per 100 cc.; in severe jaundice this may rise above 40 mg. (review, V. C. Myers and Muntwyler, 1940). The jaundiced color becomes perceptible when the plasma concentration reaches 2 mg. per cent. This generally involves impairment of the hepatic excretion or biliary obstruction; overproduction occurs in hemolytic jaundice; decreased formation in secondary anemia. Addis believed that bilirubin can be resynthesized into hemoglobin. Bile pigments are not absorbed from the intestines (Bollman *et al.*, 1926) Injected bilirubin is not stored. Its injection serves as a liver function test (Harrop and Barron, 1931). *Urobilin* is formed from bile pigment by the liver and bile passages; stercobilin is formed from urobilin by the intestinal bacteria.

Preparations.—*Ox Bile Extract*, U.S.P. (Ext. Fellis Bovis; Purified Oxgall), is an alcoholic extract of bile from the ox (Bos taurus), evaporated and mixed with starch, 1 Gm. representing 8 Gm. of fresh bile. Fresh ox bile contains about 3 per cent each of sodium glycocholate and taurocholate. Very bitter, yellow powder. Dose, 0.3 to 1 Gm., 5 to 15 grains; in pills or formaldehyde-hardened capsules; as enema, 2 per cent. *Ox Bile Extract Tablets*, U.S.P.; usual size 0.3 Gm. Various commercial preparations of *Bile Salts* are used as pills, generally 0.03 to 0.2 Gm.; or as suppositories, in the same dosage. *Sodium Cholate* (not to be confused with sodium cholalate) is a misnomer for "Plattner's Bile," a preparation of impure bile salts. Laxative dose, 0.3 Gm.; or by enema, 0.2 to 0.5 Gm.

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ANTHELMINTICS

Anthelmintics (*anti*, against; *helminthos*, worm) are remedies used against intestinal parasites. Active peristalsis tends to remove worms, as well as the other intestinal contents. Active cathartics are therefore *vermifuges*—*i. e.*, drugs which expel parasites. Catharsis alone, however, is usually only partly effective, since the worms fix themselves to the intestinal wall by suckers or hooks; or they may travel against the direction of peristalsis. They must therefore be weakened, narcotized or killed, if the cathartic is to be effective. Most drugs toxic to earthworms produce primary irritation or agitation, resulting in withdrawal of the worm from the neighborhood of the poison. This is probably an important factor in the clinical effect of vermifuges.

The paralyzants or *vermicides* may also become toxic to the host, and should therefore be used only after a positive diagnosis has been made, and then in the smallest adequate doses and under the best conditions. To be available in practice, a vermicide must either be poorly absorbable or it must be specifically toxic to the worms. All vermicides are more or less toxic to all worms, but there is some predilection. In some cases, simultaneous administration of two anthelmintics may be more additive for the worms than for the host. The subject is covered in the book of Chandler and Chopra, "Anthelmintics and their Uses," Baltimore, 1928.

The choice of the special vermicides is based mainly on clinical experience. *Oxyuris* (pinworms), which are mostly in the lower intestines, are treated by enemas of soapsuds, quassia or ferric chloride; but if they are not all reached by these, gentian violet as enteric pills, carbon tetrachloride or chenopodium oil are given by mouth. *Ascaris* (roundworms) are treated with hexylresorcinol pills, formerly with santonin, chenopodium or spigelia; *hookworm* by carbon tetrachloride, chenopodium, betanaphthol, thymol or hexylresorcinol.

Chandler and Chopra recommend carbon tetrachloride for necator (American hookworm), and this combined with chenopodium for ankylostoma (European hookworm). *Tapeworms* are difficult to eradicate because the head is imbedded in the mucosa and is not easily reached from the intestinal lumen. It regenerates the segments which are killed by the vermicide. Liquid diet and other points of technic are important. Tapeworms are treated mainly by aspidium (especially for Bothriocephalus), pelletierine (especially for Taenia), and kosotoxin. Carbon tetrachloride is fairly effective. Gentian violet enteric pills are first choice against *strongyloidiasis* (review, E. C. Faust, 1946). The most difficult parasites are the *whipworms* that reside in the cecum, where the vermicides do not penetrate. It has been suggested that these be treated by intravenous injections, *f. i.*, of neoarsphenamine (Hall and Shillinger, 1924); but this, too, would not reach the cecal contents. Surgical removal may be the only effective treatment.

The effectiveness of anthelmintics may be studied on dogs by comparing the number of worms removed with those remaining, as found by autopsy (Hall and Shillinger, 1924). This needs to be checked by clinical trials, since the conditions of the alimentary tract are different. Preliminary tests may be made by exposing ascarids or other worms to the agents *in vitro*. All clinical anthelmintics are markedly toxic to *earthworms*. These may therefore be used to determine whether a substance has any anthelmintic value, and to compare the relative activity of different samples of a drug, although Lamson and Ward, 1936, claim that the toxicity to earthworms does not correlate closely with pig's ascarids. The "*eelworms*" of vinegar (anguillula aceti) were used as test objects by Rath, 1929, and by Belehradek and Necasova, 1929. In any case, *in vitro* tests need not parallel the comparative clinical value of different anthelmintics; since this often involves factors other than simple vermicidal efficiency, such as toxicity for the patient, irritation of the intestines, etc.

The following are some of the more important results observed on earthworms (Sollmann, 1918): Highly effective are aspidium, betanaphthol, carvacrol, chenopodium oil, chloroform, dibrom and dichlorbenzol, pelletierine and thymol. Santonin is also highly active in the presence of a suitable solvent (mixture of bile salts and sodium bicarbonate). Fresh pumpkin and squash seeds are quite efficient, the active principles being soluble in water and injured by boiling. Fairly efficient are granatum, kamal, kousso. Spigelia is weak.

The routine of the anthelmintic treatment should aim to secure optimal conditions for toxicity to the parasites, and the minimum of toxic effects for the patient. Preliminary fasting and purgation may be employed to clear away protective mucus. These measures also tend to weaken the patient and to increase absorption. *Chenopodium oil and carbon tetrachloride* are quite as effective against ascaris and hookworm and are less toxic to the patient, without elaborate preliminary treatment, merely making the preceding meal light and not too bulky, and with a minimum of fat. The drug may be administered three hours after this meal. For *tapeworm*, however, it is advisable to precede the drug with two days of liquid diet, and to administer a purgative (a tablespoonful of magnesium sulfate in a glass of water) on the preceding night and on the morning of the administration. The anthelmintic is taken fasting, early in the morning, followed two hours later by the second dose of magnesium sulfate. It appears better to take the anthelmintic as a single dose rather than in divided doses, since the former insures the highest concentration, and divided doses increase the absorbing surface. Breakfast may be eaten an hour later. In case of failure, several days should elapse, one or two weeks for tapeworm, before repeating the treatment; this applies even if the failure is due to loss of the anthelmintic by vomiting Pregnancy does not greatly increase the risk of anthelmintics (animal experiments, Savignoni and de Maria, 1933), but they should be avoided if possible.

Catharsis.—Safe doses of the vermicides usually depress but do not kill the parasites, and these would recover if left in the intestines. It is necessary, therefore, to follow the vermicide by an active cathartic. This also prevents further absorption of the drug and so diminishes the toxicity. It should be timed according to the location of the parasites: for hookworm and ascaris it may be administered with the anthelmintic; for tapeworm, one or two hours later; and for oxyuris and trichuris, two or three hours later. Magnesium sulfate (a tablespoonful in a glass of water) is satisfactory as cathartic, and the magnesium may perhaps further depress the worm. There is no harm in giving calomel with the magnesium sulfate. Castor oil produces a satisfactory catharsis, but it has been feared that it may increase the absorbability of most of the anthelmintics, since these are more soluble in oil. This is doubtful, but as it has no advantage over Epsom salt, the latter is generally preferred.

Adjuvant Condiments.—Mustard, pepper or onions are recommended to be used freely in the preparatory supper. These are in fact fairly active vermicides, and while not sufficiently powerful alone, they aid materially the medicinal vermicides (Sollmann, 1918).

CARBON TETRACHLORIDE

This methane derivative, CCl_4, is an effective and inexpensive agent for the treatment of hookworm and tapeworm infection. It is less effective against other worms. Since it is slowly absorbed from the alimentary tract, and is itself somewhat cathartic, the anthelmintic dose lies much below the ordinary toxic dose (probably about as 1:50), and even minor disturbances are generally absent if a saline cathartic is given. Some patients complain of headache, however, and death has occurred, so that its use is not recommended. If the drug is absorbed, it acts similarly to chloroform, being somewhat narcotic, and leading to serious degenerative changes in the liver. With gastric administration this degree of absorption is reached only in the slow intestinal progress of herbivorous animals. Rabbits and sheep, for example, are very susceptible. In man, serious toxic symptoms have occurred from large doses administered against ascaris, and from the inhalation of the vapor when it was used for drying the hair after shampooing; it is a hazard in its use as a cleaning fluid ("*carbona*"), although there is no danger in the use of small quantities for sponging. It is also used extensively as a nonexplosive fat solvent. Industrial poisoning in rubber factories was described by Hamilton, 1915. If ventilation is inadequate, the vapor resulting from the use of carbon tetrachloride may cause serious effects, such as local dermatitis, acute inflammation of the eyes and respiratory tract, and even pneumonia. Chronic intoxication may result in liver degeneration and nephritis. A concentration in the air of 0.1 per cent by volume is considered dangerous; heating the vapor is especially dangerous, since phosgene may be produced by temperatures over 200° F. It is used in fire extinguishers ("*pyrene*"), but this is inadvisable, as fatalities have occurred from the phosgene production in confined space (reference, J.A.M.A., *101:* 1239). *Industrial dermatitis* has been reported from prolonged contact (L. Schwartz, 1939). Good results have been reported from its application to dermatophytoses and burns (G. M. Fasting, 1944).

Use as Anthelmintic.—Carbon tetrachloride is especially effective against necator, less potent against ankylostoma, fairly effective against ascaris, but inferior to chenopodium or santonin. It has little effect against tapeworm.

The anthelmintic action of carbon tetrachloride was demonstrated on dogs by Hall, 1921, and confirmed on man by Nicholls and Hampton, 1922, and especially by S. M. Lambert, 1922. The first dose is usually completely effective in about 95 per cent of the patients. Its effectiveness against *intestinal protozoa* is low, although paramecia are killed instantly by 1:3000 solution.

Administration as Anthelmintic.—Carbon tetrachloride is an active irritant, and is therefore administered in gelatin capsules. Patients should be warned to swallow the capsules promptly, and not to break them in the mouth. The adult dose is 2 to 3 cc. (30 to 45 minims); for children, 0.13 cc. (2 minims) for each year of age up to fifteen years. It should be taken fasting, in the morning. A purgative dose of magnesium sulfate is administered two or three hours after the anthelmintic. It is also advisable to administer a laxative dose of the salt on the preceding day. A test dose of chenopodium oil (3 cc., 45 min.) may be given a week after the carbon tetrachloride to check the success. The administration of the tetrachloride should not be repeated within three weeks. The first dose generally removes 95 per cent of the hookworms, sometimes all. A diet rich in calcium (milk) and carbohydrates should be used for several days in advance, to protect the liver. Fats, including castor oil, and alcohol favor absorption and should not be taken while the drug is in the intestinal tract.

Chandler and Chopra, 1928, suggest the use of carbon tetrachloride and chenopodium oil together, as more effective and less toxic. For ankylostoma or ascaris they recommend 2 cc. of the tetrachloride and 1 cc. of chenopodium, and for necator 3 cc. of the tetrachloride and ½ to 1 cc. of chenopodium, the latter administered in capsules, and the carbon tetrachloride in milk, which diminishes gastric irritation.

Klotz, 1934, reported that adsorption by the tetrachloride on charcoal retains its anthelmintic potency but diminishes its toxicity.

Fate.—The *absorption* is at first rapid, then slow. It is usually stated that alcohol increases the clinical toxicity, presumably by hastening absorption; but in animals this occurs only with 95 per cent alcohol; it is not altered by 50 per cent. Magnesium sulfate also had little effect

(Wells *et al.*, 1925). Large doses are excreted with the fat of the feces. The absorption, distribution and excretion have been studied in dogs by B. H. Robbins, 1929.

Clinical side actions occur especially if the drug is given without the cathartic, or on a full stomach, so that the sojourn is prolonged. Fat appears especially deleterious. The most frequent symptom is headache, which may persist for several days. Many patients become sleepy. Nausea and vomiting are rather exceptional. The immediate toxicity is low because of the limited absorption; even 250 cc. administered to dogs may cause only slight and transient symptoms. The effects on the circulation and central nervous system are similar to those of chloroform. Like this, tetrachroride irritates the skin on local application, and the respiratory mucous membranes if the vapor is inhaled. The serious and fatal effect, hepatic degeneration, occurs later, sometimes with ordinary therapeutic doses, especially in patients addicted to alcohol, in whom the liver may have been impaired. With such patients, it would seem advisable to make a preliminary test of the functional capacity of the liver. Ascaris infections also give a high toxicity, partly by obstructing the evacuation of the drug, and partly by diminishing the resistance of the patients (Tomb and Helmy, 1933).

Toxicity for Animals.—Rabbits succumb to 4 cc. per Kg., while dogs are apparently uninjured by 25 cc. per Kg., by mouth. Administration of 3 to 25 cc. to dogs on alternate days for fifteen weeks caused no loss in weight or other disturbance of health, but autopsy showed early cirrhosis of the liver (P. D. Lamson and Wing, 1926). The difference depends on absorption, for both animals are about equally susceptible to inhalation. Puppies are more susceptible than full grown dogs. Monkeys are uninjured by 1 to 5 cc. by mouth, every two or three days for twelve to sixteen doses. It is much more toxic for cats than for dogs, causing more damage to the liver and kidneys, but the latter are not injured by therapeutic doses. The administration of sugar with the carbon tetrachloride diminishes the damage to the liver in cats, but not in dogs. Sodium citrate diminishes the toxicity by increasing the alkalinity of the intestine, while hydrochloric acid increases the toxicity; magnesium sulfate decreases the toxicity by purgation (A. C. Chandler and Chopra, 1926); fats and alcohol increase the toxicity (Lamson, 1923). Pregnancy does not increase the toxicity as it does with chenopodium.

Bromosulphthalein retention is the most suitable test for hepatic dysfunction in mice (J. Casals and Olitsky, 1946).

Toxic Effects after Oral Administration.—These consist especially in severe damage to the liver, shown by liver-function tests, diminished coagulability of the blood, bilirubinemia, and by the pathological changes at necropsy. There are also nervous symptoms, and death occurs after several days (Lamson, 1923).

Hepatic degeneration, similar to that of chloroform, arsphenamine and phosphorus, is likely to follow especially on continued administration, but three-fourths of the liver may be necrotic in dogs after a single dose of 4 cc. per Kg., and in cats the liver may be practically completely destroyed by 0.25 cc. per Kg. Cats are also more susceptible to renal damage. The liver injury is greatest about forty-eight hours after administration; if this period is survived and the drug is not repeated, rapid repair sets in and after a few days little evidence of the injury remains. Continued administration to dogs, 3 to 15 cc. on alternate days for fifteen weeks, leads to atrophic hepatic cirrhosis (Lamson and Wing, 1926; Chandler and Chopra, 1926). Tracer experiments with deuterium show that the liver fat comes from fat depots. With severe intoxication, acute or chronic, the parenchymatous degeneration extends to other organs; cellular infiltration predominates if the intoxication lasts over eight days in rabbits (Binacalani, 1934). The liver injury prevents the formation of bile salts (Bollman and Mann, 1936). It raises the cholesterol level of the blood (Dervillée *et al.*, 1938). The guanidine level rises in this as in other acute (but not chronic) hepatitis (J. T. Cutler). The degree and permanence of the hepatic lesions on *multiple exposures of rats depend* on the intervals (Cameron and Karuna-Ratne, 1936; Rao, 1936). They range from acute necrosis to hobnail fibrosis, similar to human cirrhosis. The spleen also increases by two to ten times the normal size. Severe progressive macrocytic and hyperchromic anemia develops with bone marrow changes similar to those of pernicious anemia. There is early leukocytosis, later leukopenia (Higgins and Stasney, 1936). Recovery occurs three to six weeks after discontinuing (R. W. Heinle, 1938). Repeated oral administration to mice results in *hepatomas*, resembling those that occur spontaneously or with o-aminoazotoluene (J. E. Edwards and Dalton, 1943).

Toxic effects of inhalation are more acute and chiefly narcotic (Lehmann, 1911; he also investigated other aliphatic fluorine derivatives). Excessive concentrations may be fatal by respiratory or cardiac failure (Lamson). A nearly fatal result occurred from its inhalation when it was used to remove adhesive tape near the face (F. M. Chandler, 1936). Hepatitis has also followed its inhalation in a confined space (Butch, 1932). Three cases of *acute nephrosis* from inhalation, one fatal, are reported by J. R. Forbes, 1944. H. Smetana, 1939, found renal symptoms in nearly a fourth of the toxic cases; more frequently when the exposure was repeated (review, Corcoran *et al.*, 1943). *Toxic concentrations of the vapor* are especially important in industry. Continuous exposure during the whole working day is safe with to 100 parts of vapor per million (by volume); 1000 ppm is safe for peak periods of half an hour, if the total average per day does not exceed 100 ppm; 1600 ppm is safe only for ten or fifteen minutes. Animals exposed continuously to 50 to 400 ppm may at first develop some hepatic and renal degeneration, but they soon recover even with continued exposure, and the regenerated cells have a greater resistance, so that the liability to hepatitis decreases. This may explain the infrequency of cirrhosis in industrial workers. The limiting concentration of 100 ppm has a faint odor to persons coming from fresh air; if the odor is more than faint, the concentration is too high for safety (H. F. Smyth, 1935; Smyth *et al.*, 1936). The recognition and treatment of carbon tetrachloride poisoning are discussed by the Council of Industrial Health, 1946, J.A.M.A., *132:* 786.

Dietary protection against hepatic injury and its consequences is secured to a considerable degree by richness of carbohydrate protein and calcium, and limitation of fats. This holds also for other hepatites.

High glycogen content appears to render the liver cells more resistant to degeneration. High carbohydrate is also important to counteract the tendency to hypoglycemia. It may be advisable to administer insulin with sugar. The renal damage is not decreased (Chandler and Chopra, 1926). Liver injury from chloroform increases with the lipid content of the liver cells (Goldschmidt *et al.*, 1939). The relation to *meat diet* is not so clear. However, Messinger and Hawkins, 1940, showed that feeding with proteins as well as carbohydrates protects against liver injury by arsphenamine. Miller, Ross and Whipple, 1940, found that proteins protect against the hepatotoxic action of chloroform, and showed that this is due chiefly to methionine, and, to a less degree, to cystine. Brunschwig *et al.*, 1945, report protection against carbon tetrachloride liver injury of rats in decreasing degree by sodium thioglycollate, glycollate, glutathione, thiomalate, malate and cysteine; not significantly by aspartic acid, acetate, glutamate, methionine, choline and cystine. Beattie *et al.*, 1944, report successful treatment by *methionine* of a patient with carbon tetrachloride liver enlargement. Daily doses of 3 to 5 Gm. of methionine also protect against trinitrotoluene hepatitis (J. H. Eddy, Jr., 1945); but recovery from infectious hepatitis was not significantly accelerated by such dietary measures (Hoagland and Shank, 1946). In rats inhaling about 300 ppm for six months, methionine and low fat diet protect better against renal injury than against hepatic cirrhosis (P. György, Seifter *et al.*, 1946). Various vitamins, including p-aminobenzoic acid, do not protect (Forbes *et al.*, 1942). Calcium administration was introduced by A. S. Minot and Cutler (J. T. Cutler, 1932) to combat the effects of increased guanidine concentration of the blood which they consider responsible for the toxic phenomena. This is their reason for restricting meat. Cantarow *et al.*, 1938, confirm that the calcium therapy reduced the mortality in cats by half. Chandler and Chopra, 1926, found the toxicity increased by ammonium chloride, decreased by sodium citrate. *Administration of liver preparations* also tends to decrease hepatic necrosis and cirrhosis (H. C. Forbes, 1938).

Carbon Tetrachloride, U.S.P. (Tetrachloromethane, CCl_4), is a clear, colorless fluid. Odor resembles that of chloroform. Not inflammable. Slowly decomposed by light and by various metals in the presence of moisture. Very slightly soluble in water (1:2000). Miscible with alcohol, oils and fat solvents. Dose, 2 to 3 cc., 30 to 45 minims, with caution! *Carbon Tetrachloride Capsules,* U.S.P.; the usual size contains 1 cc.

Other chlorinated hydrocarbons are also potent anthelmintics. Tetrachlorethylene is the most important. *Chloroform* has been used clinically, but is absorbed too readily, as its solubility in water is eight times that of carbon tetrachloride. Other chlorinated aliphatics are used as cleansing agents and lacquer solvents, for instance, *di- and trichlorethylene* and *tetrachloracetylene.* All are liable to produce hepatitis.

Tetrachloroethylene, $CCl_2{:}CCl_2$, is highly *effective* against hookworm, somewhat less against necator than against ankylostoma. It has promise against trichuris and intestinal flukes. It is less efficient against other worms. It is not advised against ascaris, as it causes their migration. It is *safer* than carbon tetrachloride and at least as effective. Therapeutic doses do not damage the liver, but there may be some narcotic effects, giddiness, vomiting and drowsiness; it is therefore well to keep the patient in bed during the treatment. It does not raise the guanidine level of the blood as does the tetrachloride. However, Christensen and Lynch, 1933, claim depression of the heart and respiration and visceral changes. Coma similar to that from chloroform may occur, but is rare (J. H. Sandground, 1941). The drug was introduced by M. C. Hall and Shillinger, 1925, as anthelmintic for dogs. The *clinical dosage* is 1 to 3 cc. in soft capsules of 1 cc. or on a lump of sugar. An ounce or ounce and a half of magnesium sulfate should be administered on the preceding evening, and again two hours after taking the capsules. The patient should fast until the bowels have moved. Fats and alcohol should be avoided. One dose often suffices, and it should not be repeated in less than ten days. It may be given with chenopodium oil. It forms phosgene on exposure to the air, and broken capsules should not be used (Lamson, Robbins and Ward, 1929; Maplestone and Chopra, 1933; Christensen and Lynch, 1933; H. F. Garrison, 1934).

Tetrachloroethylene, U.S.P., is a colorless liquid, boiling at about 121° C. not inflammable; practically insoluble in water, soluble in alcohol and in oils. Average dose, 3 cc. *Tetrachloroethylene Capsules,* U.S.P., usual sizes 0.2, 1 and 2.5 cc.

Carbon tetrachlorethane is also used against hookworm (Maplestone and Mukerjii, 1933).

Trichloroethylene is used especially against oxyuris. It is administered by mouth, fasting, 0.1 cc. per year of age, in 200 cc. of Magnesium Citrate Solution (W. H. Wright *et al.*, 1937). The total should not ordinarily exceed 1.2 cc.

CHENOPODIUM OIL

The volatile oil distilled from American Wormseed is effective, especially against round-worm, hookworm and intestinal amebas. Against hookworms, it is equally or more successful than thymol, and is less unpleasant. It does not require a preliminary fast, and does not usually make the patient sick (Coutant, 1916). It is relatively safe, although the full doses are sometimes toxic. It should not be given to debilitated patients. Children are much more susceptible to poisoning than are adults. The activity, both anthelmintic and toxic, is due chiefly to *ascaridol,* the less volatile fraction, which constitutes 45 to 70 per cent of the oil (Malloy, 1923). The less volatile fraction is less irritant and less emetic (M. C. Hall and Hamilton, 1918).

Historical.—Wormseed was used by the American Indians, probably before Columbus. The oil was employed in medical practice against ascaris, but was not esteemed highly unitl it was introduced against hookworm by Schüffner and Verwoort, 1913.

The anthelmintic efficiency is high against all kinds of nematodes, and low for tapeworms. It is about equal to carbon tetrachloride against necator and more effective than carbon tetrachloride against ankylostoma and ascaris. A single dose of 2 cc. of the oil for adults removes 90 to 95 per cent of the necators, and effects complete removal in 40 per cent of the patients. With ankylostoma it removes 80 to 85 per cent of the worms, with complete removal in 30 per cent (*Hookworms:* Schüffner and Verwoort, 1913; Darling *et al.*, 1918; *Ascaris:* Bruening, 1906, 1912; M. C. Hall and Foster, 1917. *Other parasites:* Darling *et al.*, 1918; Hall and Shillinger, 1924). The effects on the worms are similar to those of santonin, viz., peripheral stimulation, followed with large doses by paralysis (Trendelenburg, 1915).

Amebic Dysentery.—Chenopodium administered as for hookworm promptly relieves the clinical symptoms of subacute and chronic amebic dysenteries and causes the disappearance of the amebas from the stools. Chenopodium may be successful in patients and carriers that have resisted emetine because of the encysted amebas. Relapse may occur, but not oftener than with ipecac (E. L. Walker and Emrich, 1917; Barnes and Coot, 1918).

The administration of chenopodium oil against hookworm does not require preliminary fasting or purging, but the oil is nauseating and must be given in divided doses, 3 capsules of 0.5 cc. (10 minims) at intervals of an hour; 1 cc. with the same spacing is not quite safe. An ounce of saturated solution of magnesium sulfate or a tablespoonful of castor oil is given an hour before the last dose, as the ordinary dosage does not kill but merely paralyzes the worms. Both purgatives decrease rather than increase the toxicity of chenopodium oil (Hall and Shillinger, 1924). If inordinate depression or somnolence or any toxic manifestations set in, the dosage should be discontinued and the saline purge administered at once. The course is repeated every three to five days. until the parasites have disappeared from the feces. The dosage for children is 1 drop per year, on sugar. The treatment may be contraindicated during the fever or acute gastrointestinal inflammations. *Ascaridol* has about twice the potency of the oil and could be used in half the dosage, with less irritation, but it is expensive.

Dosage against Ascaris.—For children, 5 to 10 drops of the oil are given on sugar two or three times a day for two days and followed by a tablespoonful of castor oil (Levy, 1914).

Minor Side Effects of Therapeutic Doses.—Nearly a third of the patients react by some degree of dizziness, nausea, vomiting, tingling in hands and feet, temporary deafness or general depression (D. A. Roth, 1918). Dizziness and nausea are the most frequent. Vomiting, sometimes with streaks of blood, occurs in about 16 per cent of the cases, and increases with the dosage (Darling *et al.*, 1918). *Deafness* occurs in 20 per cent. It varies in intensity from a disagreeable after-effect to complete bilateral loss of hearing, lasting usually for a week to several months, but in rare cases still present after two years (Roth, 1918; Oppikofer, 1919). Oka, 1929, attributes the injury primarily to degeneration of the spiral ganglia, with changes in the Nissl bodies.

Severe human intoxications are exceptional and generally attributable to gross overdosage. However, severe poisoning has been described after two doses of 10 minims, four hours apart (Coutant, 1916), and death has occurred after two treatments with 3 cc. within a week. The symptoms consist in extreme dizziness, prostration, headache, somnolence, stupor. The face is flushed, the respiration is slow; the pupils are sluggish; the hearing is disturbed; the eye muscles may be paralyzed. Albuminuria is frequent. About 70 per cent of the severe cases terminate fatally with rapid stupor and coma, tachycardia, convulsions, rarely hemiplegia. Death occurs usually after two or three days of coma (Levy, 1914; Darling *et al.*, 1918). The *treatment* consists in purgatives and stimulants (Motter, 1914).

Toxic effects on animals have been studied especially by Salant and his co-workers, 1910 to 1916. The toxicity varies greatly, even with intravenous injection. It is increased by starvation, diminished by abundant diet. Cumulative effects have also been observed. Intact animals first show depression of the higher centers, then convulsions. There is a cardiac fall of blood pressure and organ volume, with slowed heart and decreased vagus irritability Somewhat larger doses also decrease the rate and amplitude of the respiration, independently of the circulation. Peristalsis is diminished, by intravenous injection, as well as in the excised intestine. The depression is antagonized by barium, but not by pilocarpine. Renal irritation is also evidenced. Caffeine antagonizes the respiratory depression; epinephrine and digitalis the cardiac depression (Salant and Livingston, 1916). Oral and hypodermic administration may cause *renal disturbance* in rabbits fed on oats, but not in those fed on carrots (Salant and Bengis, 1917). The *mucous membranes* are severely inflamed and remain hypersensitive for five to nine days. Previous administration of fatty oils is protective (Bruening, 1912). Application of ascaridol to the mucous surface of excised small intestines of dogs increases the tonus and pendular movements. This is antagonized by atropine (H. Albert, 1934).

Oil of Chenopodium, U.S.P., is a volatile oil containing not less than 61 per cent of ascaridol, distilled from Chenopodium ambrosioides anthelminticum (American Wormseed). Dose, 1 cc., 15 minims. (Caution!)

THYMOL

This is a phenol contained in the volatile oil of thyme and in a number of other aromatic oils. Its chemical structure is allied to that of creosote constituents. Its actions are also similar to those of phenol. Its bacteriostatic efficiency is higher, restraining the growth of pus organisms in 1:3000. It is not a very active germicide. The local effects and the toxicity are relatively slight, because of its limited solubility and slow absorption. The absorption from the alimentary canal is, however, practically complete (Seidell, 1915). The solution and absorbability are favored by alcohol or oil (Schultz, 1915); these must be avoided in the therapeutic use.

Even after absorption its toxicity is but a fourth that of phenol. About half of the thymol is completely destroyed in the body (Seidell, 1915). The remainder is excreted paired with sulfuric and glycuronic acid (Blum). The symptoms are similar to those from phenol (W. H. Schultz, 1911), except that there are no convulsions, the central nervous system being primarily depressed. It is rapidly absorbed from hypodermic injections of oily solutions (Schultz and Seidell, 1912).

Uses.—Thymol has a pleasant clean taste, and a saturated watery solution makes a rather agreeable and fairly efficient antiseptic and deodorant mouth wash or gargle; lotion for discharging wounds, etc. Internally, it is occasionally employed as antipyretic and intestinal antiseptic. Its main use is an anthelmintic in the treatment of hookworm disease, for which it was introduced by Bozzolo, 1879. It is not very effective, is relatively toxic and has been displaced by other drugs. It is fairly successful in coccidioidal granuloma and has been used against trichinae, with fair results against the intestinal infection (as is also betanaphthol); but no drug is effective against the parasites in the skeletal muscle.

Thymol Test of Hepatic Function.—Administration of 0.5 Gm. of thymol to man usually results in considerable increase of the ethereal sulfate of the urine. This response is sometimes absent in hepatic disease; but it is not distinctive (M. Kahn, 1918).

Antiseptic Efficiency.—Thymol has a high phenol coefficient (25), but it is greatly impaired by the presence of organic matter. For instance, the addition of 3 per cent of dried feces reduces the activity of thymol by two-thirds, that of phenol by only one-tenth.

Yeasts, Moulds and Fungi.—Thymol is active against these in cultures (H. B. Myers) and has been tried against skin infections by these plants, with fair success.

Administration in Uncinariasis.—It is given fasting, in the total dose of 2 Gm. for adults, and the usual modifications for age, divided into three portions, taken an hour apart, best as fine powder in 5-grain capsules. The efficiency is increased by mixing the powdered thymol with equal parts of lactose or, better, sodium bicarbonate (Washburn, 1917). The thymol is preceded and followed by a saline cathartic. The treatment is repeated at weekly intervals until successful. Alcohol should not be taken while the thymol is in the intestines. Although highly effective against hookworm disease, it sometimes fails; produces some disagreeable after-effects in nearly half the patients; in a few, it causes severe poisoning; and its cost is high (Levy, 1914). The smallest wholly effective single dose is 3 Gm.; but even 4 Gm. are completely effective in only 70 per cent of the patients. Incidentally, the 4 Gm. dose removes about 30 per cent of the ascaris worms.

Thymol in Trichinosis.—When the parasites are still in the intestines, thymol may be given by the uncinaria technic. B. A. Booth, Goehring and Kahn, 1916, also report good results in one patient after the parasites had lodged in the muscles, by intramuscular injection of an oily solution (2 to 3 cc. of 6 per cent, daily for seven days; intermit and repeat). No toxic symptoms occurred.

Coccidioidal Granuloma.—In animal experiments, H. S. Sox and Dickson obtained much better therapeutic results with thymol than with other agents tested, including Sb, Cu, Bi, Hg, Pb, SCN and iodide. One human case apparently responded well to thymol administered locally (33 per cent in oil) and orally (6 Gm. daily, as 50 per cent solution in olive oil, in capsules, with meals, for twenty-four days). It was well tolerated.

Toxic Symptoms.—In man, 1 Gm. of thymol generally causes no symptoms except a sensation of warmth in the stomach. Larger doses produce dizziness, severe epigastric pain, excitement, soon followed by nausea, vomiting, marked weakness, drowsiness, quick soft pulse, tinnitus and deafness, salivation, sweating; then collapse with cyanosis, fainting, coma, low temperature, slowed pulse and respiration. Abortion may result. Rashes are not uncommon.

Thymol, U.S.P., occurs as colorless crystals; aromatic thymelike odor; pungent, aromatic taste. Very slightly sol. in water (1:1000); freely sol. in alc. (1:1) or olive oil (1:1.7); sol. in other fixed oils and in vol. oils. Liquefies when triturated with camphor, menthol or chloral. Dose, 2 Gm., 30 grains (caution!) per day divided into three doses, as anthelmintic.

Carvacrol is an isomer of thymol with the hydroxyl in the ortho instead of meta position. It has about the same effect on worms, and the same *toxicity* for rabbits: with oral administration of 1 Gm. per Kg. death generally occurs after several days (Livingston, 1920). It is somewhat more irritant.

Propylguaiacol is effective against ascaris, ineffective against tapeworm, hookworm and flukes. It is easily absorbed from the digestive tract and is quite toxic, depressing the central nervous system and the circulation (Pak and Read, 1936).

Alkyl polyhydroxybenzenes are effective anthelmintics. They cause local irritation similar to that from phenol and resorcinol and are quite toxic. Comparative studies of the series indicate that *hexylresorcinol* has a favorable balance between anthelmintic and toxic effects (Lamson and associates, 1935). It is more effective against ascaris and less dangerous than santonin or chenopodium oil (Cutting).

Hexylresorcinol as anthelmintic.—In man, 0.1 Gm. per year of age to the maximum total of 1 Gm. for adults, administered as crystals by mouth, removes 90 to 100 per cent of the ascarides, 70 to 80 per cent of the necators, 40 to 50 per cent of the trichuris; it is also effective against pinworms. It should be taken before breakfast, followed in three hours by 15 to 30 Gm. of magnesium sulfate. The single dose produces some gastric irritation, but no other symptoms or macroscopic pathologic changes. Repeated doses, however, cause inflammation and necrosis of the small intestines and microscopic injury of the liver and heart. The kidneys appear resistant (Christensen and Lynch, 1933).

Hexylresorcinol, U.S.P.: White or yellowish crystals; irritant to the skin, the alcoholic solution is vesicant. Slightly sol. in water (1:2000); freely sol. in alc., glycerin, vegetable oils. Anthelmintic dose, 1 Gm. *Hexylresorcinol Pills*, U.S.P., are covered with a tough gelatin coating. The usual sizes are 0.1 and 0.2 Gm. **Halogenated Hexylresorcinols** produce similar anthelmintic effects, and proportional local irritation. *Dibromohexyl resorcinol*, however, is not irritant and kills ascaris *in vitro* (H. H. Anderson and Sah, 1942).

Phenothiazine, used on livestock as anthelmintic against a considerable variety of intestinal parasites, has been suggested for human practice against pinworms: —4 to 8 Gm. for adults, about 4 Gm. for children above four years. 1 Gm. below this age, in capsules or in food. It is not reliably effective, however, and a fair proportion of patients have toxic symptoms. It appears to injure the bone marrow (Bercovitz *et al.*, 1943).

ASPIDIUM OR MALE FERN

The oleoresin of aspidium is the preferred drug against tapeworms. The anthelmintic action resides in several closely related substances, complex methane derivatives of phloroglucin and its homologues, with butyric radicals in ketone combination (Boehm, 1897). These are generally insoluble in water and soluble in oil. These substances are so closely related, and change so readily into each other, that our knowledge is confused; even the elementary formulae are in dispute. The most important is probably the *amorphous filicic acid.* It readily forms an inactive lactone, *crystalline filicic acid* or *filicin. Filicinic acid* is an inactive artificial reduction product of filicic acid or aspidin. The purified principles appear too irritant for medicinal use. Analogous compounds occur in several other anthelmintic drugs (rottlerin in kamala; kosotoxin in kousso).

The active constituents of aspidium (Poulsson, 1891; Boehm, 1897) are: amorphous *filicic acid* ($C_{38}H_{40}O_{12}$); aspidinin; albaspidinin; flavaspidic acid (weak); aspidin (probably from other species). The amorphous *filmaron* ($C_{47}H_{54}O_{16}$; Kraft; Jacquet; 1904) is perhaps an impure filicic acid (Schmiedeberg).

Historical.—The use of aspidium against tapeworms and roundworms is mentioned by Pliny and Galen, and its employment as abortifacient by these and by Dioscorides. It was in use during the middle ages, then fell into disuse and was revived by Valmont de Bomare, 1764. Its properties were unknown in India, where it grows abundantly (Chandler and Chopra).

Administration.—The patient should be prepared for twenty-four to thirty-six hours: A soft nonresidue diet should be given: soup, tea, milk and eggs. A saline purgative is administered on the evening before the administration. In the morning, a cup of black coffee is taken, followed by a 2 cc. capsule of the oleoresin of aspidium, repeated at intervals of half an hour to a total of 6 cc.; or less for small or debilitated patients. The last capsule is followed after one or two hours by half an ounce of magnesium sulfate in a glass of water. (Older writers caution against castor oil as dissolving the oleoresin and favoring absorption; but this is contradicted by Hall and Shillinger, 1924.) If the treatment is unsuccessful, several weeks should elapse before another administration. A single treatment with aspidium suffices for about half the cases of taenia, but some resist five or six treatments; it is but slightly effective against nematodes. Filicic acid probably paralyzes the muscles of the parasites without affecting the nerves; at least this is its action in earthworms (W. Straub, 1902). This may be utilized for standardizing filix preparations (Yagi, 1914).

Contraindications.—Aspidium should not be used on weak or emaciated patients, nor on those with gastric or duodenal ulcers; nor in pregnancy; and only with special caution when the liver, kidneys or heart are diseased.

Phenomena of poisoning may occur even with moderate doses (Sidler Huguenin, 1898), and larger doses are dangerous. Four grams of the oleoresin have produced severe poisoning, but 20 Gm. have been given without toxic effects (Drenkhaw, 1911). The symptoms involve chiefly the digestive tract, eyes and central nervous system, one or two of these generally predominationg greatly over the others. Many deaths have occurred when the dosage exceeded two drachms of the oleoresin. The milder symptoms consist in colic, diarrhea, headache, dizziness, dyspnea, yellow vision and sometimes temporary blindness. Severe cases showed delirium, violent muscle cramps, syncope, tonic convulsions and coma; often glycosuria, albuminuria and casts, and icterus; death occurs by respiratory paralysis. *Treatment* would be evacuant, demulcent and symptomatic. Recovery is slow, often with permanent blindness (Stuelp, 1904). This occurs also in animals. It is due to spasm of the retinal vessels, with subsequent optic atrophy (Harnack, 1912). Manic psychosis may develop, followed by catatonia, which may last for weeks (Westphal, 1930). In frogs, aspidium paralyzes the central nervous system, the heart and skeletal muscles; in mammals, it produces local gastro-intestinal irritation, followed by tetanic convulsions with simultaneous central and cardiac paralysis.

PREPARATIONS.—***Aspidium Oleoresin,** U.S P. (Oleoresin of Male Fern; Extractum Filicis), is an evaporated ethereal extract of the green rhizome and stipes of Dryopteris species. It should contain 24 per cent of crude filicin. It is a greenish, thick, oily liquid, often containing a crystalline sediment which is probably inert (Sollmann, 1918), but which should be incorporated before dispensing. Disagreeable taste and odor. The oleoresin preserves its activity indefinitely. Dose, 4 Gm., 1 drachm, in capsules or sweetened emulsion, or by duodenal tube, not to be repeated on the same day.

Kousso (Cusso, Brayera) consists of the pistillate flowers of Brayera anthelmintica. (The male flowers are powerfully emetic and, therefore, useless as vermicides.) Contains *kosotoxin*, related to filicic acid (Leichsenring, 1894; Lobeck, 1901). Dose, 8 to 16 Gm., 2 to 4 drachms, as infusion. It is irritant, and likely to be promptly vomited; said to depress the heart; disagreeable in action; unreliable unless quite fresh. *Kamala* (Rottlera), the glands and hairs from the fruit capsules of Mallotus philippinensis, contain Rottlerin, related to filicic acid (Telle, 1907; Semper, 1910). Dose, 10 Gm., 2½ drachms.

PELLETIERINE

This is a mixture of alkaloids obtained from *Pomegranate bark.* It acts much more powerfully on Taenia than on Ascaris (v. Schroeder, 1884; also affects higher animals). Decoctions of the bark were used as tapeworm remedy by the Romans, but the large amount of tannin (20 or 25 per cent) often causes vomiting, so that the alkaloids are preferred. These are generally given in the form of the tannates to avoid gastric irritation.

Active Constituents.—Tanret, 1878, found two active, volatile alkaloids, punicine and isopunicine. There are, further, two less active alkaloids, methylpunicine and pseudopunicine. More recently, K. Hess and Eichel, 1918, have worked on the separation of the alkaloids and determined their chemical structure.

The *administration* follows the same routine as with aspidium: two days of liquid diet; a strong saline purge on the preceding night; 0.3 to 0.4 Gm. of pelletierine tannate in the morning followed in half an hour with half an ounce of magnesium sulfate in a glassful of water, keeping the patient horizontal to diminish nausea and vomiting.

Toxic Actions.—The ordinary dose often causes mild toxic symptoms: vertigo, dimmed vision, great weakness and cramps in the legs, formication, convulsive trembling, etc. Toxic doses promptly produce mydriasis, partial blindness, violent headache, vertigo, vomiting and diarrhea, profound prostration, sometimes convulsions (Landis, 1889).

PREPARATIONS.—*Pelletierine Tannate,* U.S.P., occurs as light yellow, amorphous powder, of astringent taste, slightly soluble in water. Dose, 0.12 to 0.5 Gm., 2 to 8 grains, suspended in water.

Spigelia (Pink Root), the dried rhizome and roots of Spigelia marilandica. It is said to stupefy round-worms, but the earthworm test shows only feeble activity (Sollmann, 1918) It contains a bitter acrid resin; a poisonous alkaloid, "spigeline," said to resemble nicotine and conine; volatile oil, etc. Little is known of its action. Toxic effects, which are rare, resemble those of pelletierine. Dose, 4 Gm., 60 grains.

Areca, the fruit of Areca catechu, contains a vermicidal volatile alkaloid (arecoline). Used only in veterinary medicine. Arecoline is effective against tapeworms in dogs (Hall and Shillinger, 1924), but it is not reliable clinically It stimulates the parasympathetic mechanism (see under Pilocarpine) and therefore increases peristalsis (Paetz, 1910). *Arecoline hydrobromide* has been used locally, ¼ to 1 per cent, as miotic (smarting).

Pumpkin Seeds (Pepo), fresh or not over a year old, have some popular reputation as adjuvant to tapeworm treatment, an ounce of the seeds being eaten on the day preceding the aspidium. They are not sufficiently active by themselves, but serve to support other measures. They were investigated chemically and pharmacologically by Power and Salway, 1910, but none of the constituents had any action on the host or parasites. Weinblum, 1912, found neither alkaloids nor glucosides, and also considers the action unreliable. The earthworm test, however, shows that fresh seeds are actively vermicidal (Sollmann). This action resides in the lipoids that may be extracted by ether or alcohol (E. Rath, 1929) The seeds are but little toxic to mammals, producing only some diarrhea when 400 Gm. were fed to sheep daily for three consecutive days (Steyn, 1935).

The latex of Ficus species is fatal to ascaris *in vitro,* due to a proteolytic enzyme, "ficin," but this would generally be destroyed by the acid reaction of the stomach (B. H. Robbins, 1930; J. C. Andrews and Cornatzer, 1942). Its pharmacology and toxicology were investigated by Molitor *et al.,* 1941. It is highly effective in preventing the coágulation of blood and of milk, by digesting the prothrombase and caseinogen (Cançado, 1944).

The fresh "milk" of the cocoanut is also said to be anthelmintic. It is doubtful whether it is efficient, for intestinal parasites are abundant in the Philippine Islands, where fresh cocoanuts are consumed freely (De la Paz).

SANTONIN

This is a neutral principle from the Levant wormseed, santonica, a favorite remedy against ascaris since Dioscorides. It is effective only when joined with calomel and a saline purge. It is also used against pinworms if these have ascended beyond the reach of enemas. It is useless against taenia and not very effective against other worms. Santonin is insoluble, nonirritant and almost tasteless, and is therefore easily administered to children, but is no longer recommended, because of occasional severe toxic reactions. Doses but little above the ordinary cause "yellow vision," persisting for some hours, without other bad effects. Overdoses produce serious poisoning.

Fate.—Santonin is the lactone of santonic acid. It is dissolved in the intestine as sodium santoninate, and the greater part is eliminated unchanged in the feces. A small amount is absorbed, oxidized, and the derivatives (especially the crystalline santogenin) (Jaffé, 1890) and a colored compound (oxysantonin) are excreted in the urine (W. Marshall, 1927). This is bright yellow when acid, changing to pink when alkaline. *The color of the urine* may be confused with that of emodin (rhubarb, etc.). The emodin colors can be shaken out with ether, or precipitated by lime or barium water, while the santonin color can not.

Santonin Test of Hepatic Insufficiency.—The conversion to oxysantonin occurs in the liver and has been proposed as a functional test; administering 0.03 Gm. of santonin by mouth and comparing the alkalinized urine with an eosin solution. The color appears normally in an hour, reaches its maximal concentration in three to four hours, and disappears by the seventh or eighth hour (Fernandez, 1935).

Anthelmintic Action.—Santonin is fairly effective against ascaris; but it has a low efficiency in dogs, at best 10 per cent, even when used with purgation (Shillinger, 1927). It was formerly believed that santonin is not directly toxic to worms, but that they attempt to escape from it, and thus flee into the large intestine, from which they are evacuated by the purgative. The apparent harmlessness, however, was due to the failure to imitate the solvent action of the intestine. Solutions of santonin in dilute bile and sodium bicarbonate mixtures are highly toxic to earthworms. The irritant effect on worms plays a part in securing their expulsion, but this effect does not differ from that of other anthelmintics.

The mechanism of its action was studied by Trendelenburg, 1915, on rainworms, leeches and ascaris. It consists in strong stimulation (increased tonus and contractions) of the muscle, persisting after removal of the ganglia. The effect is not produced in anything like the same degree by other substances (although some alkaloids have a weak action), nor does santonin stimulate vertebrate muscle. It is connected with the lactone structure, as is also a depressant effect on the isolated frog heart. The convulsant effect on mammals does not depend on the lactone, but on the naphthaline nucleus.

A number of *simpler lactones* are also anthelmintic and have a similar depressant effect on the neuromuscular apparatus. The dilactone of acetone diacetic acid is effective against ascaris in cats, and practically harmless. Beta angelica lactone is somewhat irritant (von Oettingen and Garcia, 1929).

Administration of Santonin.—The dosage against ascaris is 0.06 to 0.3 Gm. for adults, and 0.01 Gm. per year for children. It may be mixed with sugar. It should not be taken fasting, since this increases absorption. A recommended routine is to eat supper at 5 P.M., administer the drug at 10 P.M., together with 0.2 to 0.7 Gm. of calomel, and follow this at 6 A.M. with a tablespoonful of magnesium sulfate in a glass of water. Fats, including castor oil, should not be taken while the drug is in the intestines. In view of the possibility of toxic effects, it should not be used unless a definite diagnosis has been made. It should not be repeated in less than seven days.

Side Effects.—Giddiness, drowsiness and nausea during the next day are not uncommon. Anomalies of color perception ("yellow vision") and of hearing occur frequently even when there are no other symptoms. The *susceptibility* to these and to more serious effects varies greatly, with many idiosyncrasies, especially with infants.

Xanthopsia.—Doses as small as 0.1 Gm. may cause "yellow vision"—*i. e.*, white light has at first a violet, then a yellowish-green hue, and these colors tint the entire field of vision. The power of seeing in dim light is also lessened. It has been demonstrated that these defects are peripheral (Knies, 1894), and the theory is advanced, based on some experimental data, that santonin impairs the reproduction of the visual purple and violet, which are at first used very rapidly. Another explanation assumes an action on the retinal violet receptors, first stimulant, then depressant (*cf.* W. Marshall, 1928). The media of the eye are not discolored (Filehne, 1900). Colored vision also occurs, but more rarely, with amyl nitrite, picric or chromic acid, and digitalis (de Schweinitz, 1899).

Uric Acid Elimination.—This is increased by santonin, as by other intestinal irritants (Abl, 1913).

Antiglycosuric Action.—Santonin decreases phlorhizin glycosuria in rabbits by raising the renal threshold, for the blood sugar level is not affected (Leulier and Roché, 1931). Santonin has been used clinically in *diabetes* (and also in *epilepsy*), but with little success.

The phenomena of severe intoxication may include vomiting, colic and profuse diarrhea, painful micturition, hematuria, albuminuria, headache and vertigo, extreme weakness, somnolence, hallucinations, finally *convulsions* (which may be unilateral), fall of temperature, coma and death (Binz, 1877; Harnack, 1901). *Treatment* would consist in evacuation, chloroform inhalation against the convulsions and stimulants against collapse.

Fatal Dose.—In children, 0.06 Gm., 1 grain, has produced serious poisoning, and two such doses have been fatal; in other cases, 0.18 Gm., 3 grains, caused only light symptoms, and recovery has occurred after 0.72 Gm., 11 grains. By adults, 0.5 to 1 Gm. and more have been taken without damage (Lewin).

***Santonin, N.F.**, is obtained from Santonica, "Levant Wormseed," the unexpanded flowerheads of Artemisia pauciflora. This also contains cineol, which has no action on ascaris (Bruening, 1912). Colorless crystals (turning yellow on exposure to light); odorless and nearly tasteless when first placed in mouth, but afterward developing a bitter taste. Very slightly sol. in water, sol. in alc. (1:43). Dose, 30 to 60 mg., ½ to 1 grain, in powder, with sugar

LOCAL VERMICIDES FOR THREADWORMS (OXYURIS)

These parasites are usually treated by the rectal injection of various irritants.

The rectum may first be washed with injections of tannic acid or bitters (quassia), to limit the secretion of mucus, and then irrigated with solutions or emulsions of salt (℥ss to pt.), aloes (ʒj to pt.) or turpentine (ʒij to pt.). W. H. Wright *et al.*, 1939, found hexylresorcinol, 1:2000, most effective, injecting a quart for adults, as much as may be retained for children; ten to twelve enemas are generally given in a three weeks' course. Mercury salts are sometimes used as injection or suppository, but are dangerous. Strong sodium chloride solution (half a tablespoonful to 4 ounces of water), injected when itching is felt, relieves this in a minute or two and kills the worms (W. P. MacArthur, 1931).

CONVULSANT POISONS

Convulsions may be caused by direct stimulation of the muscles (veratrine), or of efferent motor nerves (physostigmine, aconitine); by reflexes from strong afferent stimulation; or by stimulation of the motor centers in the cord, medulla or brain, either directly by the drug, or as a result of asphyxia. *Spinal convulsions*, as typified by strychnine and caffeine, are generally symmetrical and, when fully developed, tetanic (*i. e.*, the contractions are maintained). *Medullary and midbrain convulsions* (picrotoxin, camphor, asphyxia) are more irregular, asymmetrical and clonic (rapid intermissions). *Cerebral convulsions* (absinth) are of the epileptic type, irregular, often involving only limited groups of muscles.

STRYCHNINE AND NUX VOMICA

Strychnine, the main alkaloid of Nux Vomica, has considerable toxicologic importance. It increases the reflex excitability of the spinal cord and the medullary centers. Therapeutic doses produce a "bitter" and, therefore, tonic effect on the alimentary canal; and a limited amount of respiratory and vasomotor stimulation. Toxic doses cause characteristic tetanus, violent changes in blood pressure and spasmodic respiration. Death occurs from asphyxia and from the paralysis which succeeds the stimulations. Actions closely resembling those of strychnine are produced by a number of other alkaloids, which have little practical importance.

The **symptoms of strychnine poisoning in man** illustrate the motor phenomena: *With small doses,* there is merely a somewhat greater response to reflex stimulation, and the muscles feel somewhat more taut. As the dose is increased to 5 or 7 mg. (Hartenberg, 1913), this tightening becomes more sensible, especially in the neck and jaws; the movements become rather abrupt; and slight twitchings may appear in the individual muscles, often in the little finger. In paralysis from a high lesion (apoplexy), the paralyzed muscles may be the first to react, since they are removed from the cerebral inhibitory impulses. *With toxic doses,* these symptoms are promptly succeeded by sudden convulsions, usually following some stimulation; or the premonitory symptoms may be absent. The attack may start with a loud cry, which is usually caused mechanically, by the convulsive movement of the air, rather than by pain. The convulsions involve all the voluntary muscles of the body, including the diaphragm. The movements are at first rapidly intermittent, but become promptly tonic, resulting in a typical tetanus. Since all the muscles are contracted, the convulsions are symmetrical, and the body assumes the position corresponding to the stronger muscles, which in most situations are the extensors. Accordingly, the body is arched backward (opisthotonos), so that the patient may touch the ground only with the head and heels. The legs are adducted and extended, the feet curved inward. The arms are either strongly flexed over the chest or rigidly extended, with the fists balled. The jaws are fixed, and foam gathers at the mouth. The rigid diaphragm and the tense thoracic and abdominal muscles arrest respiration, the skin and mucosae become cyanotic and congested; the eyes are protruded, and the pupils dilated. The pulse is small, often imperceptible. The patient remains conscious and suffers severe pain from the violent contractions. The asphyxia may be fatal in the first attack. More commonly there is a remission: The tetanus lasts perhaps a minute; then the muscles relax, and the patient passes into a greatly depressed state, is very anxious and oppressed, with dry throat and thirst, sometimes sweating. This intermission lasts at most ten or fifteen minutes, when there is another attack, usually again following some slight stimulation. If asphyxia is not fatal, it is again followed by remission, and so on. The remissions, however, become progressively shorter, the spasms weaker, and the paralysis is more prominent. *Death* occurs usually in the interval after the second or fifth attack, from exhaustion and general depression. It may be preceded by asphyxial coma. *Recovery* may occur, from sublethal doses or under appropriate treatment, the convulsions and depression disappearing gradually. Animals have been observed to relapse into fatal convulsions several hours after apparently complete recovery (Sollmann), so that patients should be watched.

Reflex Nature of the Tetanus.—The principal symptoms of strychnine poisoning are referable to modified and increased reflex excitability of the spinal cord. The motor reflexes are modified so that smaller stimuli are effective, and the response even to slight stimulation is maximal, tetanic and tends to spread to all the muscles. Ordinary reflexes are increased, but the tetanus depends on the enormous exaggeration of the "startle" reflex from a sudden stimulus or fright (Cushny, 1919). This involves contraction of all muscles and therefore reversal of inhibitory reflexes in reciprocating innervations. Purely inhibitory reflexes (postural, depressor, cerebellar) are not reversed (Bremer).

Dependence of Convulsions on Reflex Stimulation.—In the lighter grades of strychnine poisoning, the convulsions occur only on reflex stimulation. In the severe grades, they may appear spontaneous, but even here they are really reflex, due to slight and accidental sensory stimulations. *Convulsions do not occur spontaneously if all sensory impressions are prevented from reaching the spinal cord;* as by dividing all the posterior roots in frogs (Hermann Meyer, 1846), together with the medulla (Hering, 1893; Verworn, 1900), or by placing the frog in a weak cocaine solution (Poulsson, 1889).

Different Forms of Stimulation.—Practically all kinds of sudden sensory stimulation may provoke the convulsions. The skin is especially sensitive. Sudden light and sound are also dangerous. Gradual stimulation is much less effective, so that a patient may support considerable but deliberate manipulation, such as artificial respiration; when a slight, but abrupt or unexpected, touch would cause an attack.

Stimulation of the exposed intestines does not cause convulsions, since these are poor in sensory fibers. *Chemical stimulation* (the application of dilute acids) not only fails to produce tetanus, but even the normal reflex is greatly diminished (Schlick, 1890). The absence of tetanus is easily explained because the slow penetration of the acid leads to a gradual instead of abrupt stimulation. The various explanations of the diminished reaction are not convincing (Baglioni, 1900 and 1909; Sano, 1908).

The Modification of the Short Reaction of Ordinary Reflexes into the Prolonged Contraction of Strychnine Tetanus.—The tetanus is a true multiple response to a *single* stimulus, for it occurs also if all reflexes but the original single stimulus are excluded; *f. i.*, tetanus occurs in a leg with a single stimulus of its divided sensory nerves, the remainder of the animal being curarized (Veszi, 1913; Buchanan, 1912; Henkel, 1913). *Electromyographic records* from frogs' gastrocnemius show that strychnine tetanus consists of groups of oscillations. The frequency of the groups depends on the temperature of the spinal cord, the frequency of the oscillations on the temperature of the muscle (D. H. Smyth, 1936).

Normal and "Startle" Reflexes.—Cushny, 1919, pointed out that strychnine has two apparently distinct actions on reflexes. A strychninized frog (0.05 mg.) responds to weak and slowly acting stimuli by reflexes of a normal coordinated character, but with lower threshold; whereas stronger and sudden stimuli produce the typical universal tetanus. This differs from normal reflexes not only quantitatively, but in that it causes the contraction of even antagonistic muscles. Cushny considers that this is a distinct reflex, which finds its physiological expression in the "startling," on sudden fright, which is enormously exaggerated by strychnine, so that it tends to displace the ordinary reflexes.

Reversal of Reciprocal Innervation.—Sherrington (1905 to 1909) showed that in a normal animal the contraction of a muscle is accompanied by the automatic relaxation of its antagonistic muscles. The reciprocal reflex is destroyed by such substances as strychnine and chloroform. Even with subconvulsive doses of strychnine, all reflex stimulations result in simultaneous contraction of all the muscles, including the antagonist; with chloroform, they result in simultaneous relaxation. The vasomotor system presents analogous phenomena (Bayliss). Subsequent work, however, showed that purely inhibitory reflexes, such as the vagal inhibition of the heart, are not reversed by strychnine, but only mixed reflexes with a weak augmentory component. The distinction is merely quantitative in that strychnine increases the augmentory component of reflexes more than it does the inhibitory component; in other words, it decreases and equalizes the *chronaxia* of the various groups of spinal reflexes (Bremer; Dusser de Barenne). Direct application of strychnine to *peripheral nerve fibers* also shortens their chronaxia, and this effect is the greater the slower their normal chronaxia (Lapicque, 1929; Bremer and Rijlant); but it is questionable whether this analogy can be transferred to the central action, which is probably not exerted on nerve fibers. Direct application of dilute strychnine solution to frog sciatic nerve slows conduction and blocks the fibers in their trunks (Peugnet and Coppée, 1936). This explains the apparent "*curare action.*"

Cholinesterase is inhibited by strychnine (D. Nachmansohn, 1938). It has been suggested that this raises the excitability so that the discharge from any nerve cell "fires" all the other cells with which it connects.

Central Location of the Tetanizing Action.—The distinction between the possible sites of convulsant action illustrates the general method of experimental pharmacology. Most of these experiments can be carried out more conveniently on frogs, but they can also be demonstrated on mammals (review, Dusser de Barenne, 1933).

The Action Is Localized in the Spinal Cord.—(*a*) *The peripheral motor apparatus* is excluded by section of the nerve trunk, which arrests the convulsions in the corresponding muscles (Johannes Mueller, 1844). Conversely, no convulsions occur if strychnine is injected directly into a muscle—say the leg—provided that the leg is first ligated so that the poison can not reach the general circulation. (*b*) If this experiment is modified so that the nerve is not included in the ligature, the absence of convulsions also proves that strychnine does not affect the *peripheral sensory apparatus* (Magendie, 1819).

(*c*) *The brain and medulla oblongata* are not essential to the convulsions, for these occur in frogs in which these centers have been destroyed. (*d*) *The posterior root ganglia are also not concerned;* for typical tetanus can be obtained by direct stimulation of the cord, when all the posterior roots have been cut in frogs; in dogs even when the afferent fibers from these ganglia have completely degenerated after section (Sherrington, 1898). Nor does the localized application of strychnine to the exposed posterior root ganglia produce any effects (Dusser de Barenne, 1910).

(*e*) *Action on the Spinal Cord.*—By exclusion, the strychnine action is located somewhere in the spinal cord. From much ingenious investigation, it appears that both the motor and sensory portions of the cord must be poisoned to obtain the typical strychnine convulsions.

Methods of Anatomical Isolation.—The basic experiments in this direction were made by Hermann Meyer in 1846: After cutting away the entire posterior columns of the spinal cord, he found that strychnine does not produce tetanus, even if the remaining cord is touched. If the ablation is confined to a part of the cord, the corresponding muscles do not participate in the convulsions. This seems to indicate that the action is located in the posterior and not in the anterior columns. However, as pointed out by Verworn, 1900, the proof is not conclusive, for the operation produces too much shock and, besides, destroys all the physiological relations of the motor cells. Similar objections apply to all anatomical methods, so that these can not furnish conclusive evidence. It was therefore necessary to have recourse to physiological means.

Segmental Application of Strychnine to the Spinal Cord—Houghton and Muirhead, 1895, basing themselves on the earlier and imperfect work of A. J. Spence, 1866, attempted to utilize the fact that impulses go from the sensory cells of the cervical segments of the cord to the motor cells of the caudal segments, and *vice versa*. By destroying the circulation and applying strychnine locally to the exposed cord it is therefore possible to make impulses pass either through a poisoned sensory cell to an unpoisoned motor cell; or through an unpoisoned sensory to a poisoned motor cell. If strychnine is restricted to the cervical half of the cord and the foreleg is stimulated in this frog, the hindleg participates in the convulsions. When the hindleg is stimulated, there is no convulsion. Analogous observations have been made on mammals (Ryan and McGuigan, 1911); on frogs with the sensory paths paralyzed by phenol (Baglioni, 1900); and on the excised nervous system of toads (Baglioni, 1909).

The observations were interpreted as proof that strychnine acts essentially on the sensory mechanism of the cord, and that the motor cells are unessential. However, these results are obtained only when the cervical cord is poisoned. If the strychnine is applied to the lumbar cord, the convulsions do not spread at all to the cervical segments, but remain confined strictly to the poisoned area (McGuigan and Becht, 1914). Furthermore, if the *entire* animal is poisoned by small doses of strychnine, the same phenomena are observed as in the Houghton-Muirhead experiment; namely, minimal stimuli applied to the forelegs produce general convulsions, whereas the same stimuli applied to the hindlegs produce only local contractions. The Houghton-Muirhead phenomenon may therefore be explained by the more easy spreading of impulses in the caudal than in the cephalic direction. (The subject is reviewed by McGuigan, Keeton and Sloan, 1916.)

Localized application to the ventral and dorsal surface of the exposed spinal cord of mammals and frogs has furnished more definite information (Dusser de Barenne, 1910 and subsequently):

1. When the application is restricted to the ventral surface of the cord, no perceptible symptoms are produced.
2. When it is restricted exclusively to the dorsal surface, there is no tetanus; but, instead, a characteristic syndrome, comprising sensory disturbances (paresthesias), increased reflexes, and incoordinate asymmetrical twitchings. These "dorsal symptoms" are sharply localized on the skin according to the level and site of application to the cord; the skin areas being identical with the "dermatomata" defined by anatomic-physiologic isolation methods. They occur even after the division and degeneration of the posterior root fibers.
3. Typical tetanus occurs only if *both* the sensory and motor tracts are poisoned. *F. i.*, if the strychnine is applied dorsally to the arm region, and ventrally to the leg region, then stimulation of the leg causes only normal reflexes (unpoisoned sensory to poisoned motor); stimulation of the arm causes tetanus of the legs (poisoned sensory to poisoned motor) in which the arms do not participate (poisoned sensory to unpoisoned motor). This experiment (which was confirmed by Beritoff, 1913) indicates that both the sensory and motor cells must be poisoned to obtain the typical tetanus.

Cerebral Centers.—No effects are perceptible on ordinary observation. The *action currents* of the brain, as with other convulsant poisons, exhibit peculiar "attacks" of rapid potential changes, not localized, but apparently spread over the entire cortex (M. H. Fischer, 1932). Their significance is not clear, but they are probably mediated through the thalamic nuclei: local application of concentrated strychnine sulfate solution to small areas of the brain surface causes the subjacent cortical cells to send out spikes of unified impulses which "fire" (stimulate) the cells to which these send axons, in a much larger but strictly delimited portion of the cortex. This in turn causes sensory disturbances, hyperesthesia and hyperalgesia, by "firing" cells in the thalamic nuclei serving the sensibility of the parts of the body to which the sensations are referred. This method is employed for sensory localization in the cortex (Dusser de Barenne, 1916 to 1941; review, W. S. McCulloch, 1944). *Local strychninization* of the leg, arm or face areas in the precentral or postcentral *motor cortex* of monkeys produces marked hyperactivity both in the cortex and in the corresponding *thalamic nuclei* (electro-thalamograms; Dusser de Barenne, 1937). The periodic potential discharges occur one or two minutes after the application, and are accompanied by localized or generalized convulsions, which may be inhibited by the local application of 5 per cent phenobarbital (Gozzano, 1936). The excitability of the motor cortex to electric stimulation is increased by the direct application of strychnine (or of picrotoxin). The rhythmic twitching may show the localization of electrical stimulation of the centers. It is not easily abolished by general anesthesia (Bickeles and Zbyszewski, 1913). The action is on the gray matter, for it disappears on ablation, and does not occur on direct application to the white matter (S. S. Maxwell, 1906; Baglioni and Magnini, 1913).

The *sensory cortex of the brain* responds to localized application of strychnine by large and rapid voltage fluctuations at the site of application and in the functionally related areas. This method shows that the cortical sensory area of the chimpanzee is a large region both in front and behind the central fissure (Dusser de Barenne, 1939; P. Bailey *et al.*, 1940). Application of strychnine to the "silent area" of the brain does not produce evident symptoms (Amantea, 1913). The *psychic centers* are evidently not affected by strychnine, since consciousness is not disturbed until the onset of asphyxial coma. However, *direct injection of strychnine into the hypothalamus* causes rage and fear response in cats (Masserman, 1938). Local application of dilute strychnine solutions to the lateral *cerebellar cortex* produces increased extensor tone. Application to the anterior lobe causes alternate dorsal and ventral flexions (F. R. Miller, 1926).

Special Senses.—Strychnine (2 to 3 mg.) increases the sharpness and field of vision for all colors (Dreser, 1894; confirmed by Kayser, 1929, with the liminospectroscope), and also the olfactory sense. The sense of touch is little, if at all, affected. These actions are central. In the eye it also probably acts on the retinal ganglion cells, the effects being obtainable unilaterally by injection into the temples or under the conjunctiva. It has been employed to arrest the progress of optic atrophy amaurosis (Nagel, 1871), sometimes with temporary improvement; ½ to 1 cc. of a ½ per cent solution (2.5 to 5 mg.) being injected into the temple.

Therapeutic Uses of the Spinal Action.—The increased postural tonus of skeletal muscles prompted the use of strychnine and nux vomica as a *tonic* in conditions of fatigue and general weakness; but this would be of no real benefit, and requires doses that verge on the toxic. It was also employed with the idea of taking the place of exercise to preserve muscular nutrition in *functional paralyses*, but ordinary doses would be useless, and larger doses could only be harmful. This probably holds true also for its employment to stimulate the spinal centers in *incontinence of the bladder and sphincters*, and against sexual impotence.

Indirect Results of the Motor Actions.—The increased activity of the muscles brings about several secondary results, such as pain, asphyxia, increased metabolism, disturbance of temperature, tendency to rise of blood pressure and quickening of pulse; early post-mortem rigor. The asphyxia in turn produces its characteristic phenomena.

Effect of Convulsants on Temperature.—All convulsant poisons (santonin, picrotoxin, strychnine) produce changes in heat regulation. Small doses cause increased heat loss and a slightly smaller heat production. Larger doses increase metabolism, through muscular action, and hence increase heat production, which is accompanied by a further increase of heat loss. Paralytic doses diminish the heat production greatly. The temperature is accordingly variable: small doses tend to lower it; moderate convulsive doses would increase it; paralytic doses lower it greatly. The heat loss is particularly conspicuous in small and young animals, while larger animals tend to show a rise of temperature with moderate doses.

The **medullary actions of strychnine** are analogous to its effects on the spinal cord, consisting in a more or less violent and convulsive exaggeration of the reflex excitability, particularly of the respiratory and vasomotor centers, followed by paralysis with toxic doses. These effects are modified by the coexistence of asphyxia. The medullary stimulations are marked and violent with convulsive doses. With therapeutic doses, they are so slight that they can not be demonstrated with certainty, either clinically or experimentally. The therapeutic use of strychnine as a respiratory or circulatory stimulant was doubtless due mainly to the uncritical transfer of the results of convulsive doses to therapeutic doses.

Respiration.—In animals, therapeutic doses of strychnine increase respiration mainly by acceleration (Cushny, 1913). This is due to increased excitability of the center, and indirectly to the increased movements. The increase of respiration is not always conspicuous, on account of the variable excitability of the respiratory center. Clinically, it is practically absent (Newburgh, 1914: Edsall and Means, 1914; Higgins and Means, 1915, 4.5 mg. hypodermically). It is presumably more conspicuous when the excitability is partly depressed, as in anesthesia or morphine poisoning (Hanzlik, 1923); but is practically not very efficient even then (R. Meissner, 1923). Similarly, strychnine causes a distinct and fairly lasting improvement of respiration when this has been depressed by cerebral compression (Loevenhart *et al.*, 1918). With toxic doses, the respiration is spasmodic, arrested during the tetanus, accelerated immediately after, and depressed during the intermissions. The respiratory tetanus is reflex, like the muscular tetanus; it does not occur if the posterior roots have been divided (Pike *et al.*, 1919).

Metabolism.—The increased muscular tone or convulsions result in increased consumption of oxygen and output of carbon dioxide, and increased use of glycogen. The increase of gaseous metabolism is observable even with therapeutic doses (Edsall and Means, 1914). The asphyxia may also cause hyperglycemia and glycosuria. The convulsions lower the *oxygen tension of the blood.* The *carbon dioxide* tension may be raised by the accumulation of *lactic acid,* from the tetanus with inadequate oxygen supply, provided that the glycogen store is adequate (Lusk, 1916). The *urinary acidity* increases (Dietrich and Ebster, 1928). Strychnine does not alter the *oxygen and CO_2 dissociation curves* of blood *in vitro* (W. Ludwig and Ebster, 1927). The *guanidine* level of the blood is not raised by strychnine and other convulsants acting at different levels of the central nervous system, more than would correspond to the renal insufficiency and blood concentration (Ander and Emerson, 1938).

The *epinephrine output* of the adrenal glands is increased by convulsive doses of strychnine. Struggling and asphyxia also increase the output, but G. N. Stewart and Rogoff, 1919 and 1920, found a marked increase, to ten times the normal, by large but subconvulsive doses. Harmon and McFall, 1929, failed to confirm this. *Blanching of the skin* of strychnine-poisoned frogs has been attributed to sympathetic stimulation (A. Hoffman and Wertheimer, 1927).

Therapeutic Doses on the Circulation.—These produce either no effect whatever, or a slight (10 to 20 mm.) rise of blood pressure, fairly well sustained. The rise is rather more marked in the diastolic pressure. Direct observation of the vasomotor center may also, but exceptionally, show a slight and doubtful stimulation; but in asphyxia, the same doses (0.05 mg. per Kg.) cause intense vasomotor stimulation (Pilcher and Sollmann, 1915). These effects (aside from asphyxia) are so inconstant and small that they could be accidental. The cardiac contractions are not changed. Clinical observations on the blood pressure and heart rate, in health and in various diseased conditions (cardiac diseases, fever, etc.), give similarly negative or inconclusive results, even when rather large doses (6 mg. every hour) are used (Newburgh, 1915; Lucas, 1914). Positive results must be viewed with caution. The pulse flow (the change of blood flow during the pulse cycle) is also unaffected in man by 3 to 6 mg. (Hewlett, 1917).

Convulsive Doses.—While small doses of strychnine have but little effect on the circulation, convulsive doses cause a high rise of blood pressure due chiefly to the muscular spasm which mechanically raises the intra-abdominal pressure and increases the peripheral resistance (Abreu and Woodbury, 1943). This is accompanied by direct and reflex stimulation of the sympathetic and parasympathetic centers, including the medullary and spinal vasomotor centers. It is followed by fall of blood pressure through asphyxial depression of the vasomotor center and heart. The partly asphyxiated heart is very susceptible to permanent arrest by vagus stimulation, which is a common cause of death.

This description applies almost equally well to the effects of convulsions produced by any other cause; and particularly to asphyxia. These are both present in strychnine poisoning, and must be contributory factors. However, they are not the only cause of the rise of blood pressure; for this occurs when convulsions are excluded by complete curarization and when asphyxia is prevented by artificial respiration.

The *vein pressure*, which is also unchanged by therapeutic doses, rises during tetanus, indicating cardiac insufficiency (Capps and Matthews, 1913). In man, also, the vein pressure is unaltered by therapeutic doses (G. Rosenow, 1919).

Vascular Areas.—During the strychnine rise of pressure, all the splanchnic vessels contract, while those of the skin (Wertheimer and Belezenne, 1897) and cerebrum (Roy and Sherrington, 1890) dilate. The vessels of the pia mater and retina are constricted (Hirschfelder, 1915).

The vasomotor center is greatly stimulated by convulsive doses, independently of the convulsions or asphyxia. Very large doses (above 1 mg. per Kg.) depress and paralyze the center. Subconvulsive doses may produce slight stimulation in decerebrate cats (Pilcher and Sollmann, 1915; van Esweld, 1930). *The vasomotor reflexes* from the carotid and aortic sinus are sensitized by small doses.

Vasomotor Convulsions.—In curarized animals, the rise in blood pressure occurs spasmodically (S. Mayer, 1872), and can be brought on by reflex stimulation, like the convulsions in ordinary animals. The same dose is required to produce the convulsant and the vasomotor actions. This supports the view that the action of strychnine on the medullary centers is essentially identical with its action on the spinal centers.

Spinal Vasomotor Centers.—Attempts to demonstrate these have usually been vitiated by shock. Langley, 1919, 1924, showed that with spinal curarized cats—provided the blood pressure is good—convulsive doses of strychnine produce a large rise of blood pressure, almost as great as if the spinal cord were intact; this occurs also after the adrenals have been excised. The spinal vasomotor centers therefore play a large part in the vasoconvulsive action of strychnine, at least in cats. The margin between the ineffective and effective dose (about 0.5 mg.) is narrow. Excessive doses decrease the excitability, and tend also to lower the pressure by peripheral mechanisms.

Paralysis of Autonomic Ganglia.—Large doses of strychnine and brucine, like curare, paralyze all autonomic ganglia. This can be antagonized by stimulant doses of nicotine.

Heart.—The opinion that strychnine is a "*cardiac stimulant*" prevailed widely among clinicians, but this term was used loosely and does not necessarily imply that the drug stimulates the heart directly, but merely that it improves the pulse. In fact, strychnine has no effect whatever on the heart in therapeutic doses with *living animals.* Convulsant doses cause some stimulation of the ventricles (Wiggers, 1916). When perfused directly through the *excised* heart, the effects are first stimulant, then depressant (Hedbom, Igersheimer, 1905; Burridge, 1928); but the necessary concentration could not be attained in life. *Perfusion of the cardio-inhibitory center* produces stimulation (cardiac slowing, in turtles; A. D. Bush, 1919).

Therapeutic Use of Medullary Stimulation.—The supposed circulatory and respiratory actions of strychnine led to its use in collapse (fainting, trauma and hemorrhage; fevers; depressant poisons, alcohol, anesthetics, coal-tar derivatives, snake venom, etc.) and in exhaustion of the respiratory center (pneumonia, phthisis); but it is not effective. The clinical studies of Newburgh, 1914, and Lucas, 1914, were entirely negative.

Depressant Effects of Toxic Doses of Strychnine.—The medullary and spinal functions show a curious mixture of stimulant and depressant response to strychnine; the stimulation predominating during the convulsions, the depression during the intermissions. The paralytic effects gradually increase as death approaches, the respiratory center, vasomotor center, vagus center and the cardiac muscle failing in about this order. Exhaustion and asphyxia, as well as the direct depressant action of strychnine, are important factors in this paralysis.

That exhaustion is an important contributory factor is shown by the fact that life may be greatly prolonged by preventing the convulsions through chloral or curare. The prolongation of life by artificial respiration shows the contributory action of asphyxia. However, animals die from large doses of strychnine, when exhaustion and asphyxia are both excluded, in the manner indicated. Indeed, the direct depression seems generally to be the main factor (Heubner and Loewe, 1913). The depressed animals can perform voluntary movements (Busquet and Vischniae, 1938); and depression can occur when strychnine is applied locally to the brain (F. Bremer, 1936). There is reason to believe that in the frog the paralysis of the central nervous system is caused largely by the failure of the circulation through cardiac paralysis; but this is not the sole cause, for the heart is often still beating when the reflexes have disappeared. In mammals death usually occurs before the heart has stopped.

Invertebrates.—Strychnine acts as a weak protoplasmic poison on ameboid cells, yeast, etc. Higher invertebrate animals are relatively insusceptible. Many *insects* appear quite immune, while others are only slightly injured (Juchenack and Griebel, 1910). Strychnine reverses the positive phototropic reaction of certain *aquatic larvae.* It expands the chromatophores in others. It reverses the reciprocal inhibitory innervation of the muscular system of earthworms, planarians and starfish, but not of medusae or sea anemones (A. R. Moore, 1913, 1916). Its antagonism with nicotine on *starfish* is described by Moore, 1920. Romanes, 1884, also reported characteristic effects of strychnine on jellyfish and sea urchin.

In *crawfish,* strychnine does not produce motor stimulation, but central (ganglionic) paralysis (Guillebeau and Luchsinger, 1882). This may be succeeded by temporary recovery, but this is followed by death within twenty-four hours. The paralytic and fatal effects are both antagonized by acetylcholine and mecholyl, not by nicotine. By itself, *acetylcholine* has little effect on crawfish; it quickens the heart and produces some motor stimulation Large doses are depressant. *Nicotine* causes cardiac and motor paralysis (V. Bonnet, 1937).

Phagocytosis is hindered by strychnine *in vitro* (Arkin, 1913); but the doses are very different from the clinical.

Other Peripheral Actions.—Strychnine, when used systemically, has practically no peripheral action on muscle, nerve or glands except the bitter effect.

The *local application of strong solutions* paralyzes most nervous and muscular tissues; for instance, the heart muscle, superior cervical ganglion, striped muscle-endings. The last effect (*curare action,* Lapicque, 1913) also occurs weakly in living frogs. Small doses seem to sensitize the neuromuscular junction, lowering the threshold to indirect stimulation, and delaying fatigue (Hammett, 1916). The curare effects are stronger in brucine; and methyl-strychnine may be counted in the curare group. After death, strychninized frogs cease to respond to sciatic stimulation much earlier than normally (Githens and Meltzer, 1912).

When applied to *isolated nerve,* strychnine (above 1:500,000) diminishes the amplitude of the electric response, blocking conduction before excitation. The refractory period is lengthened, the chronaxia is decreased, the rheobase is lowered by $1:10^6$, and raised by higher concentrations. The nerve is not completely restored by washing (G. Coppée and Coppée-Bolly, 1941).

Bitter Tonic Actions.—Strychnine is very bitter (perceptible in dilution of 1:400,000 to 1:100,000, according to the sensitiveness of the observer). It shares the stomachic effect of other bitters, and is therefore used to improve appetite and digestion in nervous dyspepsias, chronic gastric and intestinal catarrhs, hyperemesis, seasickness, etc., and thus favor nutrition. The increased tone of the muscle creates a feeling of vigor which contributes to the "tonic" effect. Tincture of Nux Vomica (1 cc. diluted, before meals) is often preferred to the alkaloid (1 to 2 mg.). It is often combined with other tonics (Elixir Ferri, Quininae et Strychninae Phosphatum). If the bitter effect alone is desired, the dose of the tincture may be reduced to 1 to 3 drops, which is too small to produce central effects.

It has been employed in *seasickness* as a prophylactic in conjunction with atropine (Skinner, N. Y. Med. Jour., December, 1893; Girard, 1906). The bitter and tonic effects of strychnine make it a useful adjuvant in the treatment of chronic alcoholism and other *drug habits.*

Emetic Center.—Direct application of strychnine or brucine to the floor of the fourth ventricle induces vomiting by increasing the sensitiveness to afferent impulses (Hatcher and Weiss, 1923).

Peristalsis.—Strychnine (or Extract of Nux Vomica) is often added to cathartic pills ("Aloin, Belladonna and Strychnine") with the object of improving their action, especially in atonic constipation. It stimulates the intestines on direct application (Langley and Magnus, 1907), and Yonkman, 1929, observed moderate increase of the motor activity of the small intestines in unanesthetized fistula dogs, after doses that did not increase the somatic reflexes. However, the tonus and peristalsis of the human colon, as observed on fistula patients, were not affected by the hypodermic injection of 2 or 3 mg. of strychnine (Yonkman and Singh, 1934). Toxic doses weaken or arrest peristalsis (Pollak, 1910).

Absorption.—Strychnine is promptly absorbed, mainly from the intestine. In rabbits, none of it is absorbed from the stomach proper.

Gastric Absorption.—Variable results have been obtained by different investigators when strychnine was placed in ligated stomachs. Generally, alcoholic solutions are absorbed readily, aqueous solutions scarcely at all. These results seem to depend partly on the ligation; for from unligated Pavlov's pouch aqueous solutions are well absorbed, better than alcoholic (Ryan, 1912).

Excretion.—Part of the strychnine is excreted unchanged (in man, 20 per cent or less; S. Weiss and Hatcher, 1922), mainly by the urine, practically none in the bile and feces. The excretion by urine starts within five minutes after absorption (Ipsen, 1892), and is practically completed within forty-eight to seventy-two hours (Bukunin and Majone, 1906; Hatcher and Eggleston, 1917), although traces may be found even after five days (Plugge, 1885; Hale, 1909; Kuenzer, 1914). In the remarkable case of a patient who had swallowed 15 grains and survived, Hewlett, 1913, recovered 4½ grains from the first stomach washings, and a total of 1⅖ grains from the urine, mainly between the first and tenth hours. Traces were present on the fourth, none on the fifth day. The urinary excretion of strychnine can be increased to only a limited extent, by very active *diuresis* (sodium sulfate injection); but even when this is maximal, it does not save life after doses only 20 per cent larger than the M.F.D. (Hatcher and Eggleston, 1916; S. Weiss and Hatcher, 1922).

Destruction.—At least a fourth, and often much more, of the administered strychnine can not be recovered from the excreta (Kobert); nor from the tissues of mammals, if these survive the administration three hours. The disintoxication occurs mainly in the liver, chiefly by destruction, but somewhat by storage in a loose combination (S Weiss and Hatcher, 1922). Both processes can be demonstrated by the perfusion of the excised liver. Hashed liver destroys only small amounts. The rapidity of the disintoxication is illustrated by the high tolerance to the repeated administration of sublethal doses. When the administration is spread over twelve days, twenty-five times the ordinary fatal dose does not produce any permanent damage (Hatcher and Eggleston, 1917).

Distribution in Body.—In fatal cases, the strychnine is found mainly in the blood, liver and kidneys, in frogs especially in the spinal cord, but there is no evidence that strychnine is bound by spinal cord emulsions (Dixon and Ransom, 1912).

Sojourn in the Blood Stream.—When strychnine is injected into a vein, 30 per cent leaves the blood stream within two minutes; 50 per cent within five minutes; all but traces in forty minutes. When *added directly to blood,* half or more passes into the corpuscles (S. Weiss and Hatcher, 1922).

Influence of Absorption and Channel of Administration on Effect.—Since the capacity for the excretion and destruction of strychnine is relatively great, the effect of a given dose varies with the rapidity of its absorption. Hypodermic injections are two to eight times more potent than oral administration; intravenous injections are two to three times more active than hypodermic. The effects of rectal administration approach more closely to hypodermic than to oral administration.

The toxicity of strychnine is slightly reduced by administering large quantities of fluid (Kleiner and Meltzer, 1912). Colloids have a marked retarding effect (Hatcher, 1904). Even very large doses may produce no symptoms, if the experiment is arranged so as to make their absorption gradual, as by injecting it into the ligatured limb of a guinea pig. A considerable quantity is gradually absorbed through the ligatured tissue; and if the ligature is released, after several hours, the effects will be correspondingly small.

Influence of Age.—Children are said to be comparatively insusceptible to strychnine. In old people with atheromatous arteries, large doses might lead to apoplexy. With white rats, the toxicity is greater for young than for old animals, and greater for females than for males (Poe, Suchy and Witt, 1936). Chick embryos are highly resistant, tolerating 3 mg.; while three days after hatching 0.25 mg. kill in a few seconds (E. Biocca, 1942).

Increased Susceptibility on Continued Administration.—The continuous use of strychnine does not lead to tolerance; on the contrary, the repetition of its action "educates" the nervous system to respond more readily, so that the effects are apparently slightly increased. After the repeated administration of equal tetanic doses to frogs, the spasms occur earlier and last longer (Mostrom and McGuigan, 1912). In mammals, the experiments of W. Hale, 1909, gave rather inconclusive results, some indicating increased susceptibility, others slight tolerance.

The susceptibility of different animals varies greatly. With subcutaneous administration, man, cats and dogs require about the same dose, 0.75 mg. per kilogram, to produce a fatal effect; rabbits are slightly more susceptible. Guinea pigs and frogs require about six times, and snakes eighteen times, this dose. With the frog, the spasms appear with one-sixth the fatal dose; with the guinea pig they set in only when at least 95 per cent of the fatal dose has been given. The differences for oral administration are greater. Some birds are almost insusceptible to oral poisoning, the fatal dose for chickens by mouth being 30 to 40 mg. per kilogram. *Resistance of fowls to strychnine* is due entirely to the long sojourn and slow absorption from the stomach. If the strychnine is injected hypodermically, or when it is placed in the empty stomach, the toxicity is similar to that in other animals (Heinekamp, 1924).

Temperature on Convulsions in Frogs.—Smaller doses suffice to produce tetanus when the temperature is either below or above the ordinary (55° to 75° F.). In the cold, the tetanus appears later, but lasts longer (Githens, 1913). The rapidity of onset, with large doses, rises with the temperature according to van't Hoff's law (Schlomovitz and Chase, 1916).

Toxicology.—Suicidal strychnine poisoning is not uncommon; accidental poisoning occurs from vermin bait and all too frequently from strychnine-containing cathartic pills, which young children swallow as candy. In the United States about seventy-five young children are thus killed by strychnine annually (Metr. Life Stat. Bul., Feb., 1944).

The symptoms and course of strychnine poisoning have been described under the convulsant effects.

The time of appearance of symptoms and of death depend upon the mode of administration, the condition of the stomach and other factors influencing absorption. With oral administration, the symptoms generally appear in fifteen to thirty minutes; the convulsions sometimes only after an hour or later. Death usually occurs in one to three hours, but the time may be as short as ten minutes, or as late as nine to twenty hours, or even later.

Differential Diagnosis of Strychnine Poisoning.—Strychnine tetanus may be confused with traumatic tetanus, spinal meningitis, epilepsy or hysteria. *Traumatic tetanus* is characterized by previous malaise and slow development. The convulsions begin in the jaw. The muscles remain rigid in the intermission. The course is comparatively slow. Strychnine tetanus may also begin in the jaw, but this is not so conspicuous. In rare cases of strychnine poisoning the muscles also preserve their rigidity during the interval, so that the diagnosis is sometimes difficult. When in doubt, strychnine treatment should be used. The course will clear the diagnosis. In *spinal meningitis* the diagnosis may be made by the fever and history. *Epilepsy* differs by the loss of consciousness; the reflexes are normal. In certain cases of *hysteria* the diagnosis may be impossible. Such cases should also be treated as for strychnine.

The *cause of death* is usually the tetanic arrest of respiration in the course of a major convulsion. This is aggravated by the large demand for oxygen by the violent muscular work, the cardiac strain of the high blood pressure, and the fright of the patient which disposes to ventricular fibrillation. Prevention of asphyxia by artificial respiration raises the fatal dose several times. Death then occurs by the depressant action, whose mechanism is not adequately known, but in which fatigue and acidosis play a part. Sometimes patients may die in the interim between convulsions, by this depression.

Autopsy Findings.—Death by strychnine is characterized by early and often persistent rigor. This, however, is common to all forms of convulsions, and is presumably due to the increased production of acid. The anatomical appearances are those of asphyxia and violent convulsions: venous congestion, often hyperemia of the central nervous system, and small hemorrhages; in a few cases hyperemia of the alimentary tract.

Toxic Dose.—In man, 5 to 10 mg. may exceptionally produce convulsive effects, more pronounced with 20 to 30 mg. These doses may even be fatal. The ordinarily fatal dose, by mouth, would probably be about 100 mg. With efficient treatment, patients may be saved after 250 mg.; and even doses of a gram and over are said to have been treated successfully (Hewlett). The fatal dose of Nux Vomica lies about 0.75 to 3 Gm.

Identification of Strychnine.—Strychnine may be identified in the suspected material, vomitus, or tissues (after isolation and purification) by its taste, convulsant effects on frogs and chemical tests (violet and cherry color with bichromate sulfuric acid). Its *bio-assay* on frogs is described by J. T. Priestley, 1930. Intraspinal injection in mice shows 0.00005 mg. (Spagnol, 1927). Strychnine largely disappears during *putrefaction;* although it may sometimes be found even a year after burial (Sandrich, 1884).

Treatment of Strychnine Poisoning.—Evacuation and chemical antidotes are rarely effective, since the alkaloid is quite rapidly absorbed. Effective methods of sedative treatment have been developed, especially by barbiturates, beginning with intravenous injections, which promptly suppress convulsions and thereby the asphyxia, the pain and even the anxiety. In the meantime, considerable amounts of the absorbed strychnine may be detoxicated in the liver. Such sedatives enable animals easily to survive ten times the ordinarily fatal dosage; with careful management thirty-five fatal doses have been survived. Larger amounts of strychnine require such large doses of the sedatives that death occurs by excessive narcosis, which is only weakly antagonized by the strychnine stimulation. In such desperate cases, it is advisable to run the risk of this less distressing exitus.

Routine Treatment.—Before the arrival of the physician, a chemical antidote may be administered, preferably an ounce of active charcoal in water; less desirably permanganate, iodine or tannic acid. Emetics should not be given (danger of aspiration of vomitus during convulsions). The patient should be kept quiet, isolated in a darkened room, warm, protected against sudden disturbances, reassured and calmed. As soon as possible, a barbiturate should be injected intravenously, slowly, in dosage sufficient to put the patient to sleep or to stop the convulsions; preferably sodium pentobarbital, 3 to 5 grains (0.2 to 0.35 Gm.); second choice, sodium amytal, 5 to 10 grains (0.35 to 0.65 Gm.); the dosage for children being reduced in proportion to the weight. If the convulsive condition ceases, subsequent (and smaller) doses may be administered orally, aiming merely to prevent major convulsions. If barbiturates are not available, the patient may be *lightly* etherized, not to the abolition of reflexes, but merely to relax diaphragmatic spasm (Travell and Gold, 1934). When the patient is narcotized by any of these methods, the stomach may be washed, but this is not necessary and should be attempted only if the technic is sufficiently good so that there will be no aspiration. Charcoal may be left in the stomach after the lavage, or may be administered in water by mouth if the patient is conscious. The patient should be under continuous medical surveillance for several hours. If there is any indication of respiratory spasm, gentle artificial respiration should be instituted. Kempf, McCallum and Zerfas, 1933, report uniform success from this type of treatment in eleven patients, who had taken from ½ to 12 grains of strychnine.

Chemic Antidotes.—Potassium permanganate is probably the most effective, if it is given sufficiently early. One Gm. (¼ teaspoonful) should be dissolved in a quart of warm water, carefully decanted, and administered in tumbler doses at short intervals. Iodine (15 drops of tincture in ½ glass of water) or tannic acid (teaspoon in ½ glass of hot water) merely delays absorption, but this is distinctly useful. Tea or coffee should be avoided, since the caffeine is synergistic. Charcoal or, better, caramel or fuller's earth, delays the absorption of strychnine (Sabbatani, 1914; Fantus, 1915); but their efficiency is limited.

Artificial Respiration and Gentle Movement.—Artificial respiration becomes imperative during spasmodic fixation of the respiratory muscles. It acts not merely by the air exchange, but by the gentle rhythmic movement which diminishes the fright reflex, and thus tends to inhibit the convulsions, so that life is prolonged even when strychninized animals are breathing hydrogen (Meltzer and Gies, 1903). However, in so far as respiration is impeded, breathing of oxygen aids survival (Osterwald, 1900). Practically, it is usually not important. Narcotic concentrations of carbon dioxide also arrest strychnine convulsions (Ryan and Guthrie, 1908). Merely keeping the hands gently on an animal, even without rhythmic movements, allays the convulsions by reducing the liability to fright reflexes (Sollmann).

Aliphatic Narcotics.—The efficiency of choloroform, chloral, ether, paraldehyde, amylene hydrate, etc., against strychnine convulsions has long been known; but their application was limited by the difficulty of administering them during the convulsions, and of maintaining them at a safe level for a sufficient time between the convulsions. Chloroform and chloral (2 Gm. of the latter followed in half an hour by a third gram if necessary) presented the special danger of cardiac depression and delayed hapatitis. *Ether* has again been advanced by Travell and Gold, 1934, who find that it may save dogs from ten times the fatal dose of strychnine, hypodermically; but the etherization must be light, and indeed the lighter, the more severe the strychnine poisoning, since larger doses produce additive depression. It should not be aimed to suppress hyperexcitability, but merely to prevent respiratory fixation. This calming effect of ether persists for half an hour after the discontinuation of the inhalation.

Barbiturates.—Their advantage depends on the ease and relative safety with which sedation can be maintained. It is unsafe to prolong a major barbiturate depression longer than it is needed against the convulsive stage; the barbiturates with briefer action, such as pentobarbital, are therefore preferred, prolonging and adjusting the effect if necessary by repeated fractional doses. By this means, Barlow, 1932, saved rabbits poisoned with thirty-five fatal hypodermic doses of strychnine. Conversely, strychnine saved from not more than two fatal doses of pentobarbital. With the longer-acting phenobarbital, Haggard and Greenberg, 1932, saved rabbits from only five fatal doses of strychnine (dogs from four); conversely strychnine saved rabbits from two fatal doses of phenobarbital.

Apomorphine has been used as depressant (⅕ grain for adults, $\frac{1}{10}$ grain for infants; Marvin); but its efficiency is less than half that of phenobarbital (Haggard and Greenberg, 1932), and the emesis may add to the danger.

Magnesium sulfate, hypodermically or intravenously, diminishes the spasticity, but its margin of safety is too narrow, so that the fatality in animals is not decreased (Haggard and Greenberg, 1932; Trabucchi, 1932).

Bromide, and also iodide, are somewhat antagonistic to strychnine (Campo, 1927), but their action in safe doses is inadequate.

Morphine is theoretically objectionable, since its action on the spinal cord is synergistic with strychnine (Steuder, 1934); there is some evidence to the contrary (E. L. Porter and Lockhart, 1943). It has been employed, however, and its analgesic and euphoristic action would be useful; but it does not take the place of barbiturate. *Dehydration* by intravenous injection of hypertonic dextrose or sucrose was reported by Maloney, 1934, to increase somewhat the resistance to strychnine and picrotoxin. *Epinephrine* counteracts the cardiac depression, on local application (Januschke, 1910), but systemically, it increases the convulsive effects. *Diuresis and catharsis* are probably of little use. Very energetic diuresis (as by 2 per cent sodium sulfate intravenously) is unable to save the animal if the minimum fatal dose is exceeded by 20 per cent (Eggleston and Hatcher, 1917).

Brucine.—The action of brucine is much weaker than that of strychnine, the ratio varying with different animals. The paralytic and curare effects are relatively stronger (resembling methyl-strychnine), so that brucine is less useful therapeutically (*cf.* Dixon and Harvey, 1908).

Brom-strychnines.—The two monobrom-strychnines act similarly to strychnine, but are only ⅛ or ⅑ as effective. Dibrom-strychnine is also convulsant, but in frogs it produces mainly the curare effect (C. R. Marshall, 1912). The toxicity of a number of *strychnine derivatives* is reported by Amann *et al.*, 1943.

Vomicine, a third alkaloid of nux vomica, causes picrotoxin-like convulsions (Ruickoldt, 1930).

PREPARATIONS.—*Nux Vomica* is the dried, ripe seeds of Strychnos Nux Vomica, East Indies; yielding not less than 1.15 per cent of strychnine. It also contains less potent alkaloids (brucine, vomicine), tannic acid and fat. The name "vomica" does not refer to vomiting, but signifies "baneful." The drug was unknown to the ancients and was probably introduced by the Arabs. The first good description occurs in 1540. Strychnine was discovered in 1818. The bark contains the same principles in less amount, but relatively more brucine. It was formerly found in commerce under the name of "false angostura." Several arrow poisons are also derived from the genus Strychnos, especially the Upas Tieuté from Java. Some of the strychnos species do not contain any active principle. "*Upas*" signified "poison tree" in Malay dialect. Another arrow poison of the Indian Archipelago is derived from *Antiaris toxicaria*. These were often confused, and there are many exaggerated and fantastic legends of their toxicity (W. A. Hammond, 1863, "Physiological Memoirs," Lippincott). ***Tincture of Nux Vomica** contains 10 per cent of drug, 0.25 per cent of alkaloids, about 0.12 per cent strychnine, in about 70 per cent alcohol. Miscible with water and alc. Incompatibilities as for Strych. Sulf. Dose, 0.6 to 2 cc., 10 to 30 minims. Maximum dose, 2.5 cc., 40 minims.

The *Extract* is the powdered extract, containing 7.4 per cent of strychnine. Dose, 0.015 Gm., $\frac{1}{4}$ grain.

***Strychnine Sulfate,** U.S.P., is soluble in water (1:35), fairly sol. in alcohol. It occurs as colorless crystals or white powder; intensely bitter, even in dilute solutions. It is *incompatible* with alkalis, iodides and bromides (slow precipitation), tannin, arsenates and arsenites. (The *limits of incompatibility* with alkalis, iodides and bromides were investigated by Finnemore and Williamson, 1914, and I. Simon, 1927.) Dose, 1 to 5 mg., $\frac{1}{60}$ to $\frac{1}{12}$ grain. *Strychnine Sulfate Tablets,* U.S.P., are usually available with 0.6, 1, 1.2, 1.7 and 2 mg. ($\frac{1}{100}$, $\frac{1}{60}$, $\frac{1}{50}$, $\frac{1}{40}$ and $\frac{1}{30}$ grains). The *Elixir of Iron, Quinine and Strychnine,* N.F., contains, in the 4 cc. dose, about 0.7 mg. of strychnine sulfate, 32 mg. of quinine hydrochloride and 23 mg. of iron (as citrochloride).

Other Spinal Convulsants.—Spinal tetanus, similar to that of strychnine, is produced by caffeine, thebaine (an opium alkaloid), gelsemine, calabrine and hydrastine. It is also a late phenomenon in morphinized frogs. *Tetanus toxin* likewise induces spinal tetanus, the minor differences being due mainly to peculiarities of absorption (Froehlich and Meyer, 1915).

The Convulsive Action of Sulfonated Dyes; *Inhibitory Action of Cerebrum.—Acid Fuchsin* (Barbour and Abel, 1910) and other water-soluble, neurophilic sulfonated dyes (Macht, 1912) produce strychnine-like convulsions in frogs. In normal frogs, the tetanus occurs only after a long latent period (up to twenty hours), and requires relatively large doses. If the anterior third of the cerebrum is removed (either before or after the injection), the convulsions occur much more promptly (within thirteen minutes), and even much smaller doses ($\frac{1}{10}$ to $\frac{1}{20}$) suffice. This was originally attributed to the removal of inhibitory central impulses; but Thomas, 1920, and Syz, 1923, find that identical results are produced by injury to any part of the nervous axis, and incline to attribute the greater effect mainly to more rapid penetration of the injured tissue.

Cardiectomized Frogs.—Joseph and Meltzer, 1911, found that the late convulsant action of acid fuchsin and of morphine could be greatly hastened, and that a much smaller dose would suffice, in frogs in which the heart had been tied, the circulation of the blood being thus arrested. According to Abel, 1912, this interesting observation is explained by the peculiar distribution of the poison. The ligation of the heart prevents the dissipation of the poison in the body, and the anterior lymph hearts drive the solution directly into the communicating vessels of the central nervous system. This is therefore exposed to a much more concentrated solution. At the same time the interruption of the normal circulation, and the partial asphyxia, increase the sensitiveness of the nervous system to convulsants, for the outbreak of these is hastened even if the heart is excised *after* the drug has been injected. Meltzer, however, did not accept this explanation.

Carbon Dioxide.—This also greatly hastens the convulsions, when its tension in the air exceeds 20 per cent (Joseph, 1915). The gas also lowers the threshold for strychnine convulsions (Pilcher and Sollmann, 1915).

Tetanus Toxin.—The position of the patient in fully developed traumatic tetanus resembles that of strychnine, but the spasm is at first confined to the traumatized region, and corresponds to an exaggerated postural tonus. The site and mechanism of the action have been extensively investigated. Intramuscular injection of a small amount of tetanus toxin (a crystallizable protein; Pillemer *et al.,* 1946) into the hind leg of a cat produces tetanus confined to these muscles. The original action is central, for it does not develop if the leg is denervated before the toxin injection. The sharp localization indicates that the action is confined to the corresponding part of the spinal cord; and this implies (contrary to the view of Abel, 1934) that the toxin does not reach the central nervous system by absorption into the circulation, for in that case the whole length of the cord would be affected, as with strychnine. Indeed, intramuscularly injected tetanus toxin reaches the cord when any transport through the circulation is excluded by a large excess of circulating antitoxin. It appears that the toxin ascends in the motor nerve and is fixed in the corresponding segment and side of the cord (Acheson and Ratnoff, 1942; review, U. Friedman, 1942). No definite change in the functions of the end plates has been established (A. Perdrup, 1946).

After five days, the local contracture persists when the nerve is cut. This later phenomenon is a purely muscular contracture, without action current, located in the region of the neuromuscular junction (A. M. Harvey, 1939). It may be conceived as an increased acetylcholine effect, possibly by interference with choline esterase (Göpfert and Schaeffer, 1940).

The spasm may be combated by central narcotics (scopolamine, magnesium), or by weak curarization which blocks the excessive postural impulses but leaves the spontaneous movements, or by local anesthetics which block the afferent impulses. R. Spaeth advises barbiturates or avertin in amounts no greater than to prevent painful spasticity, continued until no longer needed for this purpose. These measures are only symptomatic and temporary. The effective treatment is by specific antitoxic serum, especially as prophylaxis. Intrathecal application of the tetanus antitoxin has proved rather disappointing.

PICROTOXIN

This non-nitrogenous neutral principle stimulates convulsive centers, especially in the medulla, perhaps also in the midbrain, and, with large doses, in the spinal cord. The respiratory and vasomotor centers and the autonomic centers are also stimulated. Picro-

toxin is perhaps the most effective antidote to serious acute poisoning by the barbiturates, and probably also other narcotics; but its actions pass readily out of control and become dangerous. They set in later and persist longer than those of metrazol, which is used more safely for the same purposes. Picrotoxin has been suggested for the convulsion treatment of schizophrenia, but the same objection holds.

Origin.—Picrotoxin occurs (5 per cent) in Cocculus indicus, the seeds of Anamirta paniculata. These have been used for poisoning fish (hence "fish berries"); to adulterate beer, in place of hops; in "knockout drops"; and as pediculocide (tincture or 2 per cent ointment). All these uses are dangerous. Picrotoxin consists of a mixture (or perhaps a feeble combination; Sielisch, 1912) of nearly equal parts of picrotoxinin and picrotin (Cervello, 1911; structural formula, Angelico, 1912). These are closely allied chemically and have identical actions, but picrotoxinin acts far stronger.

The symptoms of picrotoxin poisoning in man, with oral administration, consist in a burning sensation, nausea, salivation, cold sweat, pallor, colic, vomiting, diarrhea, slowed or quickened pulse; palpitation; shallow respiration. These are rapidly followed by confusion, stupor and unconsciousness, then, after one-half to three hours, trembling, clonic and tonic convulsions. The convulsions may be delayed for five to thirty minutes even with intravenous injections of 5 to 12 mg. They may consist of uncontrollable twitching with persistent consciousness, or full-fledged convulsions with the patient unconscious. Recovery is fairly rapid, with some depression. In fatal cases the convulsions generally pass into paralysis and death by asphyxia, after several hours.

The postmortem findings are those of asphyxia. The poison disappears rapidly during putrefaction (within one or two weeks), so that the *toxicologic analysis* must be made promptly. The characteristic effect of the isolated poison on the frog constitutes the best test. The intensely bitter taste is discernible in dilutions of 1:80,000.

Treatment.—The chemic alkaloidal precipitants would not be efficient. The best treatment would be emetics (if vomiting has not occurred), barbiturates, chloral or chloroform.

Symptoms of picrotoxin poisoning in mammals were described by J. Crichton Brown, 1875, as salivation and vomiting (central; Eggleston and Hatcher, 1915); then quiet and apathetic; then restless and apprehensive; then trembling of legs; lies on side, with efforts to stand; progressively stronger twitching of face and neck muscles; head drawn back. Then, suddenly, generalized clonic convulsions; clonic champing of jaws; closing of eyelids; marked frothing at mouth; involuntary urination; pupils dilated during the convulsions. The clonic spasms change imperceptibly to running movements, become slower, and finally cease. The animal remains quietly on its side, and then, after some efforts, regains the erect position. After a time, varying with the dose, the convulsions may recur.

The location of the picrotoxin convulsions is chiefly in the medulla oblongata, in mammals as well as in frogs. They persist after removal of the cerebral hemispheres (Gruenwald, 1909), and even on transection below the optic thalami (Pollock and Holmes, 1915), but disappear or become of the spinal tetanus type after section behind the medulla, or if the application is confined to the spinal cord. This is ordinarily eclipsed by the more potent medullary stimulation (Luchsinger, 1878). Direct application to the cerebral cortex also produces some stimulation (Maxwell, 1906 and 1907). Somewhat larger doses are required to induce convulsions in frogs after removal of the cerebral lobes, and considerably larger after removal of the midbrain. From this and reflex irritability computations it has been argued that the convulsions originate in the midbrain with minimal doses, that larger doses involve also the medulla, and very large doses extend to the spinal cord. Direct injection into the hypothalamus causes autonomic and emotional stimulation similar to that of metrazol (Wasserman, 1938). Although the convulsions appear to occur spontaneously in cycles, they are prevented by removal of the skin in frogs, so that they involve the intactness of sensory impressions (H. Schriever and Perschmann, 1935).

After-Depression.—Quantitative studies show that picrotoxin and metrazol convulsions are followed by a period of depression lasting about an hour, not accompanied by prostration or anesthesia. Loss of placement reactions indicates that it is cortical. This post-convulsive depression is not found with coramine, caffeine, cocaine or amphetamine (Dille and Hazleton, 1939).

Picrotoxin in 4:1000 solution (decidedly above the concentrations attained in life) inhibits *oxygen uptake by cat brain in vitro,* and the oxidation of pyruvate, glutamate, fumarate and succinate (J. R. Klein, 1943).

Toxic Dose.—According to Lewin, 0.03 to 0.24 Gm. of cocculus by mouth is toxic, 2.4 Gm. are fatal. Of picrotoxin, 20 mg. are toxic; the fatal dose is not known. The intravenous minimal convulsive and fatal dose varies with the speed of injection. In a schizophrenic patient, 4.5 mg. = 0.07 mg. per Kg. produced generalized clonic twitching at intervals of ten to twenty seconds, for an hour; in the same patient, 7 mg. = 0.11 mg. per Kg. resulted in a grand mal convulsion; but with another patient, 12 mg. = 0.17 mg. per Kg. had no effect whatever (G. H. Williams, Jr., 1938). Rabbits, under usual conditions of intravenous injection, are convulsed by 0.75 to 0.8 mg. per Kg., and 50 per cent are killed by about 1.2 mg. per Kg. (H. W. Werner, 1938; R. Kohn, 1938). They therefore appear to be much more resistant to the convulsions than are humans. Dogs are intermediate, and require 0.3 mg. per Kg. intravenously for convulsions, and 1.5 mg. per Kg. hypodermically for death. *Dehydration* of rabbits by intravenous injection of hypertonic dextrose or sucrose solution renders them more resistant to picrotoxin and strychnine convulsions (Maloney, 1934). *Lowering the Body Temperature* of cats to 20° to 23° C. raises the convulsive dose of picrotoxin to nearly double; the convulsions are less severe but more prolonged; the survival time is about eighteen times as long. The dose of metrazol is not materially affected; strychnine is rendered more toxic by cooling (R. T. Stormont and Hook, 1941).

Fate.—Picrotoxin, injected intravenously, disappears rapidly from the blood and cannot be demonstrated there or in the liver or muscle after two hours (Duff and Dille, 1939). It has been calculated that rabbits destroy the convulsive dose (0.8 mg. per Kg.) in about an hour. Less than 10 per cent of this is excreted by the urine

(J. M. Dille, 1938). Chistoni, 1912, claimed that the picrotoxin is excreted partly unchanged and that the *picrotoxinin* is decomposed. Picrotoxinin is somewhat more potent, 1 mg. per Kg. intravenously being fatal to 50 per cent of rabbits (R. Kohn, 1938).

Other Central Actions of Picrotoxin.—The *respiration* is stimulated before the convulsions. In cats with 0.25 mg. per Kg. intravenously, there is a latency of a quarter to half an hour, then abrupt and prolonged increase of inspiratory response to standard electric astimulation (J. A. Wells *et al.*, 1944). With convulsive doses the respiration becomes irregular during the initial twitching and arrested during the clonic spasm (Pollock and Holmes, 1915). These authors point out the similarity of the respiratory, convulsive and circulatory changes with those of epileptic attacks (Pollock and Treadway, 1913). The threshold of the respiratory center to CO_2 is lowered by coriamyrtin (Wieland, 1915). *Spasms of the laryngeal muscles* lead, in the frog, to distention of the body with air and to a characteristic cry similar to that sometimes heard with strychnine. In the early stages, the *blood pressure* may rise from stimulation of the vasomotor center. About three to eight seconds before the convulsions, the blood pressure falls, remaining low until asphyxia sets in (Pollock and Holmes, 1915). The *heart* is greatly slowed, and may even cease for a time. After division of the vagi, the heart returns almost to normal. However, some depression of the cardiac muscle is involved in this slowing. Later there may be a quickening, due partly to stimulation of the accelerator center and partly to paralysis of the vagus center and to fatigue of its endings. The *vomiting, salivary* and *sweating centers* are also excited. The sweat may be suppressed by vasomotor constriction. Direct application of picrotoxin to the floor of the fourth ventricle produces vomiting (Hatcher and Weiss, 1923). Injection into the infundibular region of rabbits results in marked fall of temperature, suppressed by narcotics, attributed to stimulation of a cooling center (F. E. Rosenthal, 1941).

Autonomic Centers.—Gruenwald, 1909, pointed out that picrotoxin produces the symptoms of parasympathetic stimulation: contraction of pupils, salivation, vomiting, slowed pulse, contraction of urinary bladder, erection, etc. These effects are central, for they do not occur after section of the nerves. They are not hindered by decerebration. In turtles, the injection of picrotoxin produces powerful tetanic contraction of the stomach. This does not occur if the vagi have been divided (F. T. Rogers, 1918). *Uterine spasms* have been observed; they are central, for they cease on destruction of the spinal cord. Picrotoxin and metrazol induce *ovulation* in rabbits, probably by stimulation of the hypophysis (C. M. Brooks *et al.*, 1940).

The lactic acid content of the brain is increased by picrotoxin and sometimes by metrazol, but much less than by cyanide (W. E. Stone, 1938). Picrotoxin produces *hyperglycemia* in well fed rabbits (D. Campbell and Morgan, 1933). It may be suppressed by many aliphatic narcotics (F. E. Rosenthal, 1941).

Fish.—The effects of picrotoxin on these, studied by E. Bachrach and Binet, 1928, differ apparently from those in mammals and frogs.

Peripheral Actions of Picrotoxin.—The *excised heart of frogs* is weakened by concentrated solutions. *Perfused vessels* of the frog are dilated, while those of the rabbits' ear are not affected. *Excised intestine* of rabbits is stimulated by small doses, paralyzed by large; *excised uterus*, gravid or nongravid, is stimulated. *Skeletal muscle* and *motor nerves* are somewhat depressed (M. Ogawa, 1928). *Hemolysis*, similar to that of saponin, is said to be produced by picrotoxin, circutoxin and phytolacca decandra.

Picrotoxin against barbiturate poisoning should be used only in cases with deep coma. The clinical data are reviewed in a Report of the Council on Pharmacy and Chemistry, 1939, J.A.M.A., *112:* 431. To this time twenty-seven cases had been treated. The results appear rather favorable. The dosage must be individualized, but generally 1 to 10 mg. should be injected by vein at intervals of one to thirty minutes until there is definite improvement, or until spastic symptoms indicate approach to dangerous overdosage.

A Picrotoxin Injection, containing 3 mg. per cubic centimeter, is administered by vein, beginning with a test dose of 2 cc., followed by 4 to 5 cc. every fifteen minutes until the patient is somewhat awakened. The dosage may then be decreased and the intervals lengthened, stopping short of muscular twitching. Severe cases may require occasional injections for two or three days. If the proper dosage is exceeded, convulsions may need to be controlled by Pentothal Sodium, 0.1 to 0.2 Gm. by vein. No picrotoxin fatalities have been reported from this treatment of clinical barbiturate poisoning, even when the dosage of picrotoxin was 200 or 300 times that which is toxic to normal individuals.

This use of picrotoxin was introduced by A. H. Maloney, Fitch and Tatum, 1931, on the basis of animal experiments. In animals, recovery begins with simple reflexes; for instance, blinking and spasmodic movements of the legs. Large doses are required, so that the animal not infrequently goes into convulsions. These are then controlled with ether. Experimental comparisons of the antidotal value of picrotoxin, metrazol, coramine, coriamyrtin and strychnine have given somewhat contradictory results (Barlow, 1938; Werner, 1938; Chakravarti, 1939; Blackwenn *et al.*, 1940). On the whole, it seems that picrotoxin is the most effective. Picrotoxin is also mutually antagonistic to chloral, paraldehyde, alcohol and bromide (Barlow, 1938; Schriever and Perschmann, 1935).

In schizophrenia, picrotoxin convulsions, induced by intravenous injection, are about as effective as metrazol treatment. They do not produce the terror characteristic of metrazol (Guy H. Williams, Jr., 1938; A. A. Low *et al.*, 1939), but the delayed action adds to the discomfort of the patient and makes control of the dosage more difficult, and it is therefore more dangerous.

Picrotoxin, U.S.P. (Cocculin), is soluble in about 350 parts of water. Average dose, 2 mg. *Picrotoxin Injection*, U.S.P.; the usual size contains 3 mg. in 1 cc. of isotonic sodium chloride solution.

Related Poisons.—Effects similar to those of picrotoxin are produced by neutral principles from a variety of other plants. *Cicutoxin* occurs in the rhizome of *Cicuta virosa*, "*Walter Hemlock*," an umbelliferous plant eaten by mistake for parsley, etc. The American species, Cicuta maculata and bulbifera, are also toxic. Poisoning may be treated by intravenous injection of a barbiturate (M. M. Miller, 1933). Cicutoxin is a complex pyrone derivative (C. A. Jacobson, 1915). Some of the *decomposition products of digitalis* (digitaliresin, toxiresin) are also counted in this group. Less important are: *Coriamyrtin* (from Coriaria myrtifolia), and *Tutin* (from Coriaria species of New Zealand, C. R. Marshall, 1910; Blackwenn *et al.*, 1940). Coriamyrtin seems to vary. That first isolated by Riban was very soluble, while Merck's is almost insoluble, but probably more active (Marshall, 1912). W. W. Ford, 1910, found that tutin combines with nervous structures, thereby losing its toxicity, but no tolerance is acquired. *Star anise,* the seeds of Illicium anisatum, of the magnolia family, produces medullary convulsions analogous to picrotoxin. They may be treated by chloral, barbiturates, chloroform and calcium lactate (B. E. Read and Kiang, 1927). *Antiaris toxicaria,* a "*Upas tree,*" has perhaps somewhat similar effects. H. N. Ridley, 1930, found that injection of the latex into toads is toxic, with slight convulsions and some peripheral actions. It had no effect on dogs, probably because it is not readily absorbed. The skin glands of *salamanders* secrete alkaloids (saladarine and others) which produce violent convulsions of the picrotoxin type. They are also local anesthetics and have various effects on smooth muscle (review, O. Gessner, 1938).

SYNTHETIC MEDULLARY STIMULANTS AND CONVULSANTS

Metrazol (*Cardiazol*), **Nikethamide** (*Coramine*) and **Hexeton** are synthetic drugs of rather unrelated composition, which produce closely similar effects, stimulating the midbrain, the medullary centers and perhaps the spinal cord. The convulsions are irregular and cyclic, and resemble those of epilepsy, picrotoxin, camphor and cocaine. Metrazol convulsions resemble those of picrotoxin more than of camphor in site of action and in absence of depressant phase. They are used in the treatment of schizophrenia. These drugs are also useful in narcotic poisoning, especially by the barbiturates, being more effective than caffeine and safer than picrotoxin. They were introduced as substitutes for camphor, to produce respiratory and circulatory stimulation in collapse, but they have little effect unless their dosage approaches the convulsive. The therapeutic claims tend to go beyond this rather limited field.

Metrazol, N.N.R. (*Cardiazol*), pentamethylenetetrazol, occurs as white crystals, freely soluble in water and in most organic solvents, with neutral reaction. Stable and resistant to most reagents. Marketed in bulk, as tablets of 0.1 Gm., and as 10 per cent sterile solution. Dose, 0.1 to 0.3 Gm., by mouth, intravenously or by vein, repeated as needed. *Nikethamide* (*Coramine*) is used orally or hypodermically as 1 to 2 cc. of a 25 per cent solution. *Icarol* is a mixture of coramine and an ephedrine derivative, intended against shock and anesthesia accidents. *Hexeton,* $CH_3.C_3H_7.C_6H_6O$, is chemically related to camphor. Its dosage is 1 cc. of 10 per cent intramuscularly, or 1 cc. of 1 per cent intravenously. Metrazol (Cardiazol) and Coramine were reviewed by F. Hildebrandt, 1937.

Convulsion Treatment of Schizophrenia.—Von Meduna, 1934, conceived the idea of treating this disease by epileptoid convulsants, on the assumption that clinically the two conditions appear to be mutually exclusive. Camphor was used at first, but was displaced by metrazol because this is more easily controlled. It is also safer than insulin hypoglycemia, which is similarly convulsive, and the therapeutic results are at least as good. Either may succeed when the other fails. Nitrous oxide, carbon dioxide and electrically induced convulsions are also effective. Severe oxygen lack as such has no beneficial effects (Horvath *et al.*, 1943).

The therapeutic results are reviewed by von Meduna and Friedman, 1939; Finkelman *et al.*, 1938, and H. H. Reese, 1939. The improvement consists in progressive restoration of contact with the surroundings, following a number of injections, and is apparently more or less permanent. The benefits are greatest in cases that have lasted less than one and a half years, and are slight after four years. (Complete remission occurs in 61 per cent of the acute cases, 37 per cent of the subacute, and 8.4 per cent of the chronic; von Meduna and Friedman.) The catatonic type responds best, then the paranoid.

Serious *accidents* are rare, the mortality being 0.3 per cent or less, perhaps because the metrazol convulsions are so brief. *Minor complications* are frequent. The most common are temporary subluxations and other dislocations and fractures. Compression fractures of vertebrae, generally multiple but not disabling, have been reported in nearly half of the patients (Polatin, Friedman *et al.*, 1939; B. T. Bennett and Fitzpatrik, 1939). Traumatic injuries may be prevented by intravenous injection of curare (A. E. Bennett, 1940) or by spinal anesthesia (Hamsa and Bennett, 1939). A death from *intracranial hemorrhage* has been reported (Roback and Miller, 1940). Monkeys show vascular damage, subarachnoid hemorrhages, and moderate *changes in cells of the cerebral cortex and basal ganglia,* but these are not always present and are not proportional to the convulsions (S. Arieti, 1941; Strecker *et al.*, 1939). Similar changes occur in insulin convulsions (K. H. Finley and Brenner, 1941). The *blood pressure* rises during the convulsions by an average of 100 mg. Hg., mainly as a consequence of contraction of skeletal muscles (it is prevented by curare) and the resulting increase of intra-abdominal and intrathoracic pressure; vasomotor stimulation plays a minor part. The pressure is also transmitted to the cerebrospinal fluid so that there is generally little increase of stress on the cerebrospinal vessels (Woodbury, Hamilton *et al.*, 1941), but the vessels of the cerebral cortex are congested even if the blood pressure is not raised (M. H. Fischer and Lowenbach, 1934). The heart rate is moderately quickened. Temporary cardiac disturbances occur exceptionally and are not serious (McAdam, 1938; Messinger and Moros, 1940); but sometimes they persist for months, indicating permanent lesions of the myocardium (Regner and Ewert, 1939). Memory defects have been reported (Zinskind, 1941). *Contraindications* to metrazol convulsions are relative. They include weakness of the bony system, for instance by prolonged bed confinement during the preceding year; acute infections; cardiovascular disease; severe intracranial injuries; exophthalmic goiter; latent tuberculosis; seropositive syphilis.

Administration.—The metrazol is given by rapid intravenous injection of a 10 per cent solution, before breakfast, in the smallest dosage that produces the typical epileptiform seizure, at least twice a week, until there is definite improvement, to be resumed if the improvement does not hold. Generally, 25 to 30 injections of "grand mal" are needed to obtain the full benefit or to decide that the treatment is useless. Rapid injection is necessary to produce the major convulsions. Subconvulsive doses cause relapse, and by their anxiety reactions create aversion and opposition. Excessive convulsions (more than three or four) may be arrested by barbiturate, avertin or ether. The pattern of motor response is set in the first injection, permitting precautions against mechanical injury. With resistant cases, Georgi and Strauss, 1937, first induce insulin shock, and administer metrazol after two hours of hypoglycemia.

The *dosage* is started with 3 to 5 cc. of the 10 per cent solution (1 cc. per 30 pounds of body weight). If this dose proves convulsive, it is maintained in subsequent injections; if not, it is increased progressively by 1 cc. at each subsequent injection, until the convulsive effect is secured. Meduna advised to keep the patients on alkali.

The *clinical convulsive response* usually sets in within a few seconds and ceases in a few minutes. *Subconvulsive doses* produce pallor, cough, anxiety, mental confusion and a few myoclonic movements. The *typical reaction* runs the following course (chiefly from Finkelman *et al.*, 1938, and H. Strauss and Landis, 1938): In two to five seconds after the rapid intravenous injection, the patient coughs; five seconds later, marked pallor of the face; then intense blepharospasm, a facial expression of fear and bewilderment, the mouth is widely opened (*a rubber wedge should now be inserted between the teeth to prevent biting the tongue*); then *myoclonic movements* of the face, shoulder, arm, sometimes on one side, then well marked rhythmic clonus; and then, some thirty seconds after the injection, the *tonic phase*, with the head retracted, the back arched, the arms and legs extended, the wrist and fingers flexed, the legs sometimes scissored, goose flesh, apnea with marked cyanosis, rise of blood pressure by 20 to 60 mm., erection and ejaculation of semen. The convulsions involve simultaneous and persistent contraction of all muscles and resemble decerebrate rigidity. After five to thirty seconds the tonus lightens to a *second clonic phase*, first at the fingers, finally at the legs, which lasts about twenty-five seconds, with decreasing intensity. The patient then relaxes, deep respiration resumes, urine is passed. The patient, who has been unconscious throughout the tonic phase, is now confused, drowsy, probably asleep. After a few minutes of rest there may be some further relatively mild convulsive movements. In about five minutes after the injection the patient may be roused, but remains confused for several hours, with complete amnesia of all the events since the injection. Exceptionally, the onset of the convulsions is deferred for fifteen to twenty minutes, with little effect in the interim (H. W. McAdoo, 1938). The *preconvulsive anxiety* is described as a feeling of impending death and annihilation, but a normal individual who underwent the experience describes the sensations as "mildly unpleasant but not alarming" (Gillespie, 1939). The patients, however, find the reaction distressing, especially with subconvulsive doses or petit mal. It is largely wiped out of memory by the amnesia of the major convulsive seizures. It may be eliminated by preliminary nitrous oxide administration, but it is not known whether this is equally effective. Metrazol convulsions are accompanied by central excitation of both divisions of the *autonomic system*, especially the sympathetic, and this occurs also if the convulsions are prevented by curare (Gellhorn and Darrow, 1939). The *blood chemistry changes* of metrazol convulsions have been studied by S. Maurer *et al.*, 1938. Therapeutic convulsive doses lower the oxygen saturation of the blood to 42 per cent (Himwich, Bowman *et al.*, 1938). The brain metabolism is diminished by the anoxia (Himwich *et al.*, 1939); its lactic acid may be increased (W. E. Stone, 1938).

Convulsions in Animals.—The description of the clinical convulsions applies also to animals, except that the spasms are more prolonged with increase of dosage, and lead to asphyxial death. In rabbits, they result in acidosis (lowered CO_2 combining power of the blood, increase of its *p*H by 0.2 to 0.4, increased acidity of the urine; S. Dietrich and Ebster, 1928). The blood sugar rises (Kastein, 1937). The convulsive response is decreased by repeated injections, by starvation, dehydration (merbaphen), and by calcium; it is increased by water retention (Kastein, 1937). The convulsions are succeeded by *depression*, probably cortical, lasting about an hour (see under Picrotoxin, Dille and Hazleton, 1939). Like picrotoxin, metrazol induces spontaneous *ovulation* in rabbits (C. M. Brooks *et al.*, 1940). *Repeated injections* on alternate days diminish the convulsant response in rats; when spaced at weekly intervals, the susceptibility is increased (Sacks and Glaser, 1941).

Subconvulsive doses of metrazol increase the susceptibility of rats to sound-induced convulsions ("*audio-epileptic seizures*"). This applies also to other drugs that increase motor excitability, such as caffeine and strychnine (K. U. Smith, 1941; Snee *et al.*, 1942).

Location of the Convulsant Action.—The character of the convulsions indicates their origin in the midbrain. They occur quite typically in cats and rabbits whose hemispheres have been removed, an operation which prevents the clonic spasms of camphor and cocaine, and modifies those of picrotoxin (H. Bertha, 1927). Direct injection into the hypothalamus causes autonomic stimulation, cyclodilatation, piloerection, urination, defecation, marked emotional excitement and increased response to faradic stimulation of the region (Masserman, 1938). The *action currents* of the cerebral cortex react alike to metrazol, cocaine, caffeine and strychnine, by "attacks" of rapid potential changes, followed by temporary inexcitability, (M. H. Fischer, 1932); the striate and precentral areas respond with four types of potential waves (J. E. Goodwin *et al.*, 1938). Metrazol, nickethamide, caffeine and strychnine in sufficient doses all cause contraction of extensors and flexors on stimulation of homolateral sensory nerve (Knoefel and Murrell, 1935). Typical convulsions occur after removal of the thalami (R. Schoen, 1926); but there is probably some action on these and on the cortex and spinal cord. Unlike strychnine, metrazol does not upset reciprocal innervation (review, Hildebrandt, 1937).

Nonconvulsive doses (0.2 Gm.) do not materially affect physical *work performance;* but fine coordination (marksmanship) is lowered (O. Graf and Muller, 1938).

Antagonistic Drugs.—Pyridine, nicotinamide, cinchophen and aminoacetic acid hinder convulsions by metrazol, but not by picrotoxin or electric stimulation. The reason is not clear (L. J. Pollock *et al.*, 1941).

Use in Narcotic Poisoning.—Metrazol with ephedrine is probably the safest effective treatment of severe but recent coma from barbiturates and other narcotics, according to animal experiments; but it is necessary to approach the convulsant dose, and the effective margin is not large (O. W. Barlow, 1938). The same limitation applies for morphine (metrazol, R. G. Smith, 1928; hexeton, Helairs, 1927). Picrotoxin is more effective but more dangerous. Coramine is much less effective (Warner and Tatum, 1939; O. Gros, 1936). They are not very useful against fatalities from volatile anesthetics (Guns, 1926). *Metrazol and strychnine together* have a more than additive effect against narcosis, indicating a different site of action (W. Koll, 1937). Metrazol may be used to test the *potency of anticonvulsant drugs* (G. M. Everett, 1946), but does not differentiate between grand and petit mal

Effects on Respiration and Circulation; Use in Collapse.—Full doses of these drugs raise the blood pressure (after a preliminary fall) and stimulate the respiration, but this occurs only when the convulsant effects are reached or approached (metrazol, Cramp, 1927; nikethamide, Massart, 1930), and their therapeutic usefulness is therefore questionable; but they are often given in severe collapse of all kinds, more with the idea of doing something than of accomplishing anything tangible.

The *respiratory stimulation* is directly central with metrazol; partly central and partly carotid sinus reflex with nikethamide (Zunz and Tremonti, 1931). Morphine depression of the respiration in man is counteracted more effectively and more promptly by metrazol, hypodermically, than by coramine (C. S. Hicks, 1935).

The blood pressure falls with moderate doses (to 10 mg. per Kg. by vein) through dilatation of the splanchnic vessels. With larger doses the fall is followed by a rise. Convulsive doses also show an initial drop of pressure followed by a rise (Haury and Gruber, 1939; Gellhorn and Darrow, 1939). *The rise of blood pressure* (which is least with hexeton, Stross, 1928) is chiefly convulsive, but some stimulation of the vasomotor center occurs with subconvulsive doses (van Esweld, 1931; Woodbury *et al.*, 1941). The coronary vessels are mildly dilated (Linder and Katz, 1941). The heart is not stimulated directly (Leyko, 1930; nor by nikethamide or camphor, S. Krop, 1944), but may be depressed, especially by intravenous injection. These drugs are ineffective against the cardiac depression of quinidine (M. H. Barker and Levine, 1928). Leuth, 1938, reported that metrazol greatly benefits some patients with complete heart block of the Adams-Stokes syndrome. Metrazol has little if any effect on *smooth muscle,* even in 1:2000 concentration (Hildebrandt, 1937).

Fate.—Metrazol is rapidly absorbed from the gastrointestinal tract and even more rapidly from the oral mucosa (H. Kuschel, 1939). It leaves the blood rapidly after intravenous injection (Werner and Tatum, 1939), so as to establish practically equal concentrations in the muscle, brain, liver and blood (H. J. Tatum and Kozelka, 1939). Its fate is not well known. It is detoxicated fairly rapidly, presumably by conjugation, in which the liver plays a part (H. J. Tatum, 1941); but this is not essential to the detoxication (O. Ridder, 1927; Fournier and Selye, 1942). Very little is excreted by the urine and bile.

Nikethamide, *Coramine,* is the diethylamide of nicotinic acid, and has some of the antipellagric action of nicotinic acid amide. The latter and nicotinic acid are somewhat narcotic. The monoethyl amide is strongly narcotic and somewhat stimulant; the diethylamide produces chiefly *convulsions* resembling those of camphor, but involving the whole central nervous system. It is imperfectly antagonistic to narcotics, and large doses cause additive depression. Subconvulsive doses produce rather lasting increase of the rate and depth of *respiration,* especially if this has been depressed by narcotics. The carotid sinus is involved in the respiratory stimulation (Zunz and Tremonti, 1931). The *blood pressure* rises, sometimes after a sudden and temporary fall. The rise is due to vasoconstriction and muscular spasm. It is slight with subconvulsive doses. Nikethamide has no direct effect on the *cardiac muscle* (S. Krop, 1944) and probably little if any on the coronary circulation. It produces feeble stimulation of *excised intestine* (F. Uhlmann, 1924). These actions would furnish little if any indication for its use in circulatory collapse. It may benefit abnormal *respiration* associated with cardiac disease (Stroud and Twaddle, 1940), and the respiratory depression of narcotic poisoning, similarly to metrazol and picrotoxin. In emergencies, a 25 per cent solution would be injected by vein, the dose (about 3 cc.) depending on the rate of injection, since it is rapidly detoxicated (review, Hildebrandt, 1937; Council on Pharmacy and Chemistry, 1942, J.A.M.A., *118*:1052).

Methylglyoxal produces severe and bizarre psychomotor activity, tonic distortions, salivation and incontinence (Fischler and Hirsch, 1927).

CAMPHOR

Camphor, $C_{10}H_{16}O$, is a derivative of terpene, $C_{10}H_{16}$, and is therefore allied to the volatile oils. Like these, it is a mild irritant and antiseptic and is often employed as counterirritant in the form of Spirit or Liniment. Larger doses produce convulsions, similar to those of metrazol, but much more persistent. They are important in poisoning, and have been employed in schizophrenia, but here it has been displaced by metrazol. Smaller doses were used to stimulate the circulation in collapse, but appear to be ineffective.

Camphor Isomers.—The structure of camphor is nearly related to p-cymol and to carvacrol (Bredt, 1893). It is asymmetric, the natural camphor being dextrorotatory, the synthetic racemic, and "matricaria-camphor" levorotatory. The actions of the three isomers appear to be qualitatively identical, and of the same order of magnitude, as to general toxicity and the response of the frog heart (Joachimoglu, 1916) and of the mammalian heart (Froehlich and Pollack, 1920, etc.). Natural and synthetic camphor are both official and may be used indifferently.

Historical.—The therapeutic employment of camphor in the Orient antedates history, but it does not appear to have been known to the Greeks, and came into use in Europe in the medieval period.

Related Drugs.—Fenchon, the characteristic constituent of fennel oil, is isomeric with camphor; it is also used as counterirritant. It is a fluid, and may be applied as such, or diluted to 10 per cent with alcohol or oil (I. Schlesinger, 1914).

Borneol (Borneo-Camphor, $C_{10}H_{18}O$) is used in the Orient. It acts similarly to camphor.

Camphoric acid, $C_8H_{14}(CO_2H)_2$, was introduced by Fuerbinger, 1888, against the night sweats of phthisis. It aroused some enthusiasm at first (literature, Fujitani, 1906), but experimental investigations gave negative results (Roth, 1911), and the clinical effects were also disappointing. Tyrode, 1908, could discover no effects of any kind. Fujitani and Roth described central and peripheral stimulant and depressant effects, somewhat different from camphor. It produces rather marked stimulation of the respiratory center in mammals. The average dose is 0.2 to 2 Gm., as powder.

Monobromated camphor, $C_9H_{15}BrCO$, acts similarly to camphor, but has no advantage, and has not been as well studied. Its average dose is 0.125 Gm., in powder or capsules. Wortix, Coombs and Pike, 1931, have used it as a standardized convulsant for cats. The convulsant dose averages 4.8 mg. per Kg. of body weight; the minimal fatal dose, 14.8 mg. per Kg. Subconvulsant doses may produce a single myoclonic twitch; small doses cause a single attack, resembling human epilepsy; large doses produce a status epilepticus, with recovery in twenty-four to forty-eight hours, or death by respiratory failure.

Allo-p-oxycamphor (*"vitacamphor"*) is claimed to be formed from camphor in the body. When injected hypodermically it is easily and quickly absorbed with little local irritation. K. Tamura *et al.*, 1932, claim that it stimulates the heart, *in situ* and excised; that larger doses stimulate the respiratory center, still larger doses the vasomotor center. Convulsions require even higher doses.

Diethylene camphor sulfonate (*"Solucamphor"*) is also claimed to stimulate the heart and respiration in chloroformed dogs (Henrijean and Waucomont, 1930).

Absorption, Fate and Excretion.—Camphor is readily absorbed from the mucous membranes and subcutaneous tissue. Hatcher and Eggleston, 1914, found the absorption more rapid from oral than from intramuscular administration. It is rapidly oxidized to *campherol*, $C_{10}H_{15}O.OH$; and this excreted in combination with glycuronic acid, $C_{10}H_{15}O.O.C_6H_9O_6$ (Schmiedeberg and Meyer, 1879). This destroys the activity of the camphor; and accordingly, Happich, 1912, claims that the toxicity is higher when glycosuric acid formation is disturbed through starvation or deprivation of oxygen. Similarly, he states that intra-arterial injections are more than twice as toxic as intravenous. *Borneol* is similarly conjugated, and has been proposed as a test of liver function. With one gram orally, normal subjects excrete 60 to 100 per cent as glycuronide within twenty-four hours (Ottenberg *et al.*, 1943).

Camphor poisoning occurs commonly from the consumption of spirit of camphor as intoxicant, or by giving "camphorated oil" to children by mistake for castor oil. The symptoms are nausea, vomiting, colic, vertigo, disturbed vision, tipsiness, excitement, panic anxiety with assault or suidical mania, confused delirium, loss of consciousness, face flushed then pale, impulsive movements, then epileptiform convulsions, which may last for many hours. They occur in man after 1.5 Gm. (Austragesillo, 1915), equivalent to 2 teaspoons of the camphorated oil, or a tablespoon of the spirit. Anuria is common. *Death* is rare in man, occurring by asphyxia and collapse. *Convalescence* may last several days or weeks; the gastric disturbance is especially persistent (illustrative reports, Stanley White, 1903; F. Baker, 1910; Koppang, 1912). The *treatment* consists in evacuation by apomorphine. If the spirit was taken, olive oil would first be given, to dissolve the camphor, so that it may be evacuated, but the oil should not be left in the stomach, or it may hasten absorption, as does alcohol. The convulsions may be controlled with barbiturates, if necessary.

The *toxic dose* varies greatly: 0.7 to 1 Gm. has been fatal to children and toxic to adults; 2 Gm. generally produced dangerous effects; but 15 Gm. have been survived (Koppang); and in an infant of eighteen months, 1 Gm. produced little if any symptoms (Miller, 1914). Benz, 1919, reported the poisoning of twenty children by the oral administration of 1 to 1½ tablespoons of camphorated oil. All were more or less convulsed, with blue-black lips, but otherwise fair color. The severe cases had lockjaw. Emesis was induced by mustard water, and all recovered promptly (twenty minutes to four hours). The *minimal fatal dose* for cats, on intraperitoneal injection, is 0.4 Gm. per Kg. (Joachimoglu).

Solvent and Place of Administration on Toxicity.—Cairis, 1914, and Carnot and Cairis, 1914, studied these on guinea pigs. With oral administration the toxicity of camphor is greatly decreased by oil. Hypodermically, oil solutions are also less toxic than alcoholic, ethereal or even watery solutions. Intraperitoneal are more toxic than hypodermic injections. Oral administration is more effective than intramuscular (Hatcher and Eggleston, 1914).

Location of the Convulsant Action.—In mammals, this is chiefly above the optic thalami, for section below these abolishes or greatly diminishes the convulsions (Albertoni, 1882; Morita, 1915). The motor cortex participates, for the direct application of powdered camphor to this region results in jacksonian and generalized epileptic spasms (Trabuschi, 1928). The spinal cord also shows some stimulation, and finally paralysis, but this does not come on until late, and is not important in mammals.

In *frogs*, the action on the spinal cord is *pronounced* and consists in a *paralysis*. This entirely obscures other actions which the drug may have higher up in the nervous system in these animals. It appears that the path for reflex impulses is blocked before that for impulses coming from the higher brain (Wiedemann, 1877; Binz, 1878). The symptoms are described by Grove, 1910.

Clinical Use of Camphor to Improve the Circulation.—The injection of camphor as a temporary "whip" to the heart, especially in collapse, is not well supported by decisive critical evidence, either clinical or experimental, and is disapproved by leading clinicians (report, Council on Pharmacy and Chemistry, 1943, J.A.M.A., *121:* 431).

Camphor was employed intramuscularly, dissolved in sterile olive oil, 1 to 2 cc. of the 10 per cent solution being repeated in ten- to fifteen-minute intervals as needed. For babies of one year, A. Jacobi advised $\frac{1}{10}$ to $\frac{1}{4}$ grain every two hours. Intravenous injection (250 to 350 cc. of 0.1 per cent in saline) is safe, but ineffective (Weintraud, 1913).

In normal individuals and in cardiovascular disease, camphor (even up to 3 Gm. hypodermically—Heard and Brooks, 1913) does not alter the blood pressure or the rate or quality of the pulse. Hewlett, 1917, failed to find any change in the blood flow of the human arm after hypodermic injection of 0.3 to 0.7 Gm. of camphor in oil.

Experimental effects of camphor on the circulation are inconstant, different investigators reporting divergent results and conclusions. Generally there is no definite response if the circulation is normal. When the heart muscle is depressed in various ways, camphor may, under favorable experimental conditions, improve the cardiac contractions and remove arrhythmias. The response is uncertain and gives only doubtful support to the claimed therapeutic action.

Blood Pressure.—The earlier investigators generally described rise of blood pressure from vasomotor stimulation. Widermann, 1877, and Stockmann, 1888, observed rhythmic rises of blood pressure, attributed to heightened reflex irritability. Stimulation of the vasomotor center, however, does not occur with therapeutic doses, but only as the convulsant effects are approached, and especially during the convulsions proper (Pilcher and Sollmann, 1915). Heathcote, 1923, found no rise of blood pressure in anesthetized animals, unless convulsions occurred. When these were prevented by removal of the cerebral hemispheres, doses up to 1 Gm. per Kg. did not raise the blood pressure. Liebmann, 1912, describes persistent fall of blood pressure, attributed to peripheral action on the blood vessels.

Excised Vessels.—Likhtacheva, 1916, reported that camphor, borneol and menthol, in 1:2500 to 1500 dilution, produce a dilatation of coronary and other vessels, strongest with borneol and weakest with camphor. More dilute solutions (1:10,000 to 50,000) have no effect on the coronary artery. Other arteries are temporarily constricted. Perfusion experiments have also been made by S. Oda, 1927.

Actions on the Heart.—Improvement has been recorded, especially of depressed hearts; but the results are uncertain.

Perfused rat heart has been found an especially suitable object for demonstrating the improvement. After being injured by cooling, electric stimulation, phosphorus, digitalis, yohimbine, or chloroform, the addition of camphor (natural or synthetic) usually increased the rate and removed arrhythmias; the tonus was generally improved; so also the coronary flow. These favorable results did not always follow; indeed, the heart sometimes became worse (Froehlich and Pick, 1920).

The hearts of most other mammals are not improved, in situ or excised, normal or depressed by various means, according to most observers (Plant, 1914; Richards, 1914; Heard, 1915); except that there is some dilatation of the *coronary vessels* (Bodo, 1928). *Excised papillary muscle* of cats is not stimulated (S. Krop, 1944).

Frog's Heart.—The effects are slight and inconstant with normal hearts, but camphor restores the beat of frog hearts arrested by muscarine (Harnack and Witkowski, 1876) or by chloral (Boehm, 1905), or fibrillated by electric stimulation or aconitine, or arrested systolically by strophanthin (Froehlich and Grossmann, 1921; Sasaki, 1921). The restoration is only transient (Plant, 1914). Joachimoglu, 1917, found a similar response to all kinds of local irritants, so that it does not appear to be characteristic for camphor. *Direct effects on the ventricular muscle* (Straub's method) were studied by Joachimoglu, 1917. Very weak solutions (1:4000) increased the amplitude slightly; depression occurred with concentrations above 1:2500 and arrest above 1:1250; the hearts may recover spontaneously. The three isomers act quantitatively alike; except that with the racemic the arrest lasts only fifteen minutes, whereas the others recover only after one and one-half to three hours. Menthols also stopped the heart, but weak concentrations did not accelerate. Junkman, 1925, found some prolongation of the refractory phase. With *ventricular strips* of turtle hearts, Plant observed slight quickening, not modified by chloral. The ultimate effects of strong solutions of camphor are depressant, weakening and slowing the beats. Camphor produces *parasympathetic paralysis in turtle auricle*, blocking the response to vagus nerve and postganglionic stimulation, and antagonizing acetylcholine, similarly to atropine (A. Collard, 1941).

Other Uses.—Camphor Spirit is a household remedy in colds and bronchitis. It was thought to be somewhat expectorant, diaphoretic and antipyretic (Binz, 1875 and 1877), but neither small nor convulsive doses are antipyretic in animals (Seymour and Boyd, 1946). The skin vessels are dilated. It was also advised in *tuberculosis*. It has been used as a nervous depressant in hysteria, epilepsy, chorea and convulsions, and as an anaphrodisiac. This rests on no rational basis.

Respiration.—The effects of nonconvulsant doses are slight and inconstant. Higgins and Means, 1915, studied the effects on man, using 0.4 to 0.5 Gm., hypodermically.

They found the center sometimes slightly stimulated with bronchodilatation and slight increase of carbon metabolism. The rate was often slowed, the volume, single or minute, was unchanged. In animals, Wieland, 1915, claims lowering of the threshold for CO_2. Isaak found it especially effective after morphine. Voegtlin and Wiggers, 1918, obtained uncertain stimulation after morphine and other depressants. Hanzlik, 1923, observed a fair increase of respiration after hypodermic injection of camphorated oil (20 per cent) in anesthetized rabbits.

Lactation.—Camphor has been used to prevent postpartum engorgement of the breast, and to induce rapid involution. There is no satisfactory evidence of this clinically. Controlled experiments in animals show no effect, even with large doses (R. R. Greene and Ivy, 1938).

Excised ureter is stimulated by the l isomer; the d is indifferent (Macht, 1918).

Skeletal Muscle.—Direct application produces a curare effect in frogs, not in mammals. Other camphors derived from various volatile oils also produce this effect (Hildebrandt, 1902).

Invertebrates.—Newly hatched squid, placed in $\frac{1}{10}$ saturated solution of camphor in seawater, responds by spasm of the mantle and contraction of the chromatophores. The stimulation appears to be in the ganglia. It is followed by paralysis, which may be overcome by nicotine (Moore, 1919).

Leech Muscle.—Joachimoglu, 1920, found that the three isomers produced quantitatively identical effects; *i. e.*, strong increase of tonus and rhythmic contractions, with concentrations of 1:1000 to 5000. Thymol acts similarly.

Local Actions.—Externally, camphor acts similarly to the volatile oils, producing mild analgesia and rubefaction, with little sensory irritation. It is applied in neuralgia, inflammations, etc., as the Spirit (10 per cent) or as Camphor Liniment (20 per cent), often reinforced with 5 to 10 per cent of chloroform or oil of turpentine. It is used (5 per cent) in oily nose sprays or nose drops.

The **irritant action** of small doses of camphor *on the digestive canal* is used *against dyspepsia*. Large doses produce *vomiting*.

Antiseptic Action.—Camphor is feebly antiseptic, the isomers being about equivalent (Joachimoglu, 1917). A saturated solution is used as stimulant *mouth wash* and *gargle*. A bit of camphor is a good preservative for hypodermic solutions, proteins, etc. (Romanelli, 1917).

Pneumonia.—Seibert, 1912, claimed that camphor reduces the toxemia and prevents the crisis, but the benefits are doubtful and the treatment has not obtained wide acceptance. Leo, 1913, preferred *intravenous injection* of the saturated watery solution. E. Stein, 1915, tried camphor against experimental pneumococcus pneumonia. He found that the different races of organisms differ in susceptibility.

PREPARATIONS:—*Camphor*, U.S.P. (Camphora), is a ketone, $C_8H_{16}CO$, obtained from the camphor tree, Cinnamomum camphora (Natural Camphor); or produced synthetically (Synthetic Camphor). White translucent masses of crystalline structure; a characteristic odor and warm, aromatic taste. It is slightly sol. in water, freely in alc., fixed and volatile oils and fat solvents. Dry camphor volatilizes readily, but its solutions are practically stable, even in open bottles (La Wall, 1909). Dose, 0.2 Gm., 3 grains, by mouth; or as 10 per cent solution in olive oil hypodermically. The solubility of camphor at ordinary temperature is 1:598 of water; 1:577 of Ringer's solution (Leo and Rimbach, 1919). The U.S.P. lists the *Spirit* (10 per cent), dose, 0.3 to 2 cc., 5 to 30 minims; *Liniment* (20 per cent in cottonseed oil; and *Water* (saturated aqueous solution, U.S.P., dose, 15 to 30 cc., ½ to 1 ounce). *Camphor and Soap Liniment*, U.S.P. ("*Soap Liniment*"), contains 4.5 per cent of camphor, 6 of hard soap, 1 of rosemary oil, in 70 per cent alcoho-

Absinth Convulsions.—The herb Artemisia Absinthium contains a volatile oil, whose chief constituent is *thujone*. This produces effects similar to those of camphor (Hildebrandt, 1901 and 1902; Matzel, 1905). Intravenous injection of 0.03 to 0.06 cc. of absinth oil, as 5 per cent alcoholic solution, into a cat or rabbit produces effects similar to those of camphor: marked excitation of the autonomic system, followed promptly by unconsciousness and general epileptiform convulsions, clonic then tonic. The convulsions wear off rapidly, and the margin between the convulsant and fatal dose is much wider than with camphor or picrotoxin. The convulsions are antagonized by phenobarbital, bromide or chloretone (Hrubetz and Pike, 1936; W. L. Sampson and Fernandez, 1939). The convulsant threshold is lowered by epinephrine, pitressin, nicotine and histamine; it is raised by parasympathetic stimulants and by large doses of nicotine and ergotamine. The parasympathetic antagonism is abolished by atropine, which has little effect by itself (H. W. Keith and Stavraky, 1935).

Absinthe and vermouth liqueurs were formerly prepared from species of Artemisia, with other aromatic oils. Continued overindulgence in "Absinthe" was believed to cause mania and other symptoms (review, I. L. Meyers, 1916). The present "absinthe" contains 0.1 to 0.2 per cent of aromatic oils, chiefly anise (anethol) and *no* thujone or acetone substances, in 40 to 45 per cent alcohol (references, J.A.M.A., 1939, *113*:1822).

MENTHOL

This is prepared from the volatile oils of various mints. It acts similarly to camphor, and is used especially locally against headache, neuralgia, itching, etc. Applied to the skin, it produces at first a cool sensation, followed by slight prickling and burning. The cooling effect is not physical, the temperature of the skin being normal or even increased. It is explained by specific stimulation of the nerve endings, for cold (Goldscheider). Alcoholic solutions are antiseptic.

Menthol has also been produced synthetically. This racemic form is about half as toxic as the natural, but its effects are similar, and its odor and taste are indistinguishable (H. Seel, 1927).

Menthol has a purely depressant effect on the frog heart (Joachimoglu, 1917).

***Menthol**, U.S.P., $C_{10}H_{19}OH$, is a secondary aromatic alcohol obtained from mint oils or prepared synthetically. It may be levorotatory or racemic. Colorless crystals of peculiar odor and warm aromatic taste. Only slightly sol. in water, freely in alc. Dose, ½ to 2 grains, B.P.; as carminative, etc. Externally, in alcohol, oils or ointments, 1 to 5 per cent, on mucous membranes and in herpes, 10 to 25 per cent on intact skin.

BULBOCAPNINE

This alkaloid induces plastic (catatonic) rigidity of the skeletal muscles by peculiar narcotic and stimulant actions, a "perturbation of the cortico-diencephalic automatism" (Bremer). It has been suggested against the tremors of the postencephalitic Parkinson syndrome.

Origin.—Bulbocapnine is an alkaloid, chemically related to apomorphine, isolated along with several other alkaloids from the tubers of Corydalis cava, a plant of the family of the "Dutchman's breeches." The actions of isocorydine, an alkaloid of the related Dicentra canadensis, resemble closely those of bulbocapnine (Waud, 1934). *Capaurine*, an alkaloid of Corydalis aurea, causes central paralysis in frogs, convulsions in mice and rabbits, and depression of cardiac and skeletal muscle (A. K. Reynolds and Waud, 1944). Of fifteen alkaloids from this family of plants, including protopine and chelidonine, only two produce catalepsy. All stimulate the uterus of guinea pigs and rabbits, and have various effects on other smooth muscle (R. C. Anderson and Chen, 1946).

Phenomena of Bulbocapnine Catatonia.—F. Peters, 1904, found that a peculiar narcotic and cataleptic condition is induced (in cats and dogs by 25 to 100 mg. per Kg.; in frogs by 20 mg.). It occurs also in monkeys (de Jong, 1934), in mice and in birds (Henry and de Jong, 1930). There is a striking plastic rigidity similar to, but not identical with, catalepsy (de Jong, 1912). The animals appear stupid and lethargic, and the muscles tend stiffly to retain any position in which they are placed. The narcosis predominates in rabbits and guinea pigs. In *man*, the postural reflexes are at first weakened, then exaggerated (de Giacomo, 1930). In *monkeys* (rhesus), small doses produce sleep, or the abstracted attitude of the "Rodin thinker." Medium doses cause the typical catalepsy. This lasts several hours. It may be measured quantitatively by the time for which the monkey remains suspended by the hand (C. P. Richter and Paterson, 1931). Large doses produce hyperkinesis with agitation and curious attitudes, and still larger doses cause an epileptoid condition (de Jong and Baruk, 1929). These phenomena are almost identical with those of clinical catatonia, the motor and psychological syndrome of dementia precox, and not with the Parkinsonian immobility (de Jong and Baruk, 1930).

Location of the Catatonic Action.—This is probably on the basal ganglia of the midbrain. Bulbocapnine does not act on the cerebral cortex (Buscaino, 1932). Electro-encephalograms show short duration volleys similar to decerebrate rigidity (A. C. Roberts and Leese, 1933). The spasticity is not antagonized by procaine in doses which relax postural rigidity. It is counteracted, however, by cocaine, 2 to 5 mg. per Kg., probably through central stimulation, especially in monkeys, which recover almost completely and immediately (Buchman and Richter, 1933). Cocaine is less effective in cats (Evrad and Spiegel, 1932). *Scopolamine* prolongs the catatonia; *carbon dioxide* inhalation exaggerates it temporarily (A. S. Peterson and Richter, 1933), or rather, it superimposes a hyperkinesis on the catatonia (de Jong, 1934). *Destruction of the optic thalami* in cats induces cataleptic phenomena and other complex symptoms (V. Neri and Chiatellino, 1939), apparently similar to those of bulbocapnine.

Antagonists.—Bulbocapnine catalepsy is inhibited by amphetamine (E. Spiegel, 1938) and by tetrahydronaphthylamine (E. F. Kerman, 1944). The latter antagonism is mutual, but bulbocapnine is not very effective against amphetamine hyperkinesis.

Peripheral Action on Skeletal Muscle.—Frog's gastrocnemius muscle, immersed in 1 per cent bulbocapnine, shortens immediately, progressing to one and a half hours and then relaxing gradually during three or four hours (Poppi, 1936).

Circulation.—Bulbocapnine lowers the arterial and venous pressure by direct action on the vessels (perfusion experiments). This is not prevented by atropine. The vasodilatation exists in all organs studied (C. E. Leese *et al.*, 1940), but is most marked in the ear, extremities and kidneys; it is slight in the intestines. It abolishes vasoconstrictor reflexes and antagonizes the pressor action of epinephrine, and the depressor action of mecholyl, but it does not decrease the response to pitressin or to histamine (H. Molitor, 1936, 1938; C. E. Leese and Fogelberg, 1937). It decreases the movements of excised *intestines*. It has no effect on blood coagulation (Molitor, 1938).

Clinical Uses of Bulbocapnine.—In man, Schaltenbrand, 1924, observed some narcosis and marked fatigue after 1 mg. per Kg. Slightly higher doses (0.1 Gm., hypodermically) have been tried in paralysis agitans, with prompt but temporary improvement (Lewy, 1926), the tremors being abolished during the administration in many cases (Mella, 1926). Others have used it in encephalitic disturbances (Hill, 1929), and in chorea (Kuttner, 1929); confirmation is needed. The plant was used against these conditions in the Middle Ages—when therapeutic observation was anything but critical. Even large cataleptic doses (to 0.6 Gm.) have practically no effect on schizophrenia (M. Ellermann, 1933) or on the catatonus in catatonic patients (de Jong, 1934). Bulbocapnine (25 to 35 mg. per Kg.) has been injected in experimental technic, to immobilize animals after operations under local anesthesia, especially on the brain (Schaltenbrand and Stanley Cobb, 1927). It may be used experimentally as preanesthetic sedative, in place of morphine-scopolamine, inducing motor sedation without impairment of respiration or circulation (H. Molitor, 1936).

Other Catatonic Drugs.—Various degrees of narcotic plastic rigidity, or at least tendency to maintain abnormal postures, occur in poisoning by cannabis indica (G. W. Henry and de Jong, 1930), by the alkaloids of *Nymphaea* and *Nuphar*, white and yellow *pond lilies* (Modrakowski, 1936), by 3-astyl 3 amino-hydrocarbostyril (N. Haysashi, 1930), and in rats and guinea pigs by morphine. Their phenomena, however, differ more or less from those of bulbocapnine, and it is doubtful whether their mechanism is the same. Harmine, barbiturates and sulfonal do not produce catatonus (Henry and de Jong, 1930).

CAFFEINE, THEOBROMINE, THEOPHYLLINE AND OTHER METHYLXANTHINES

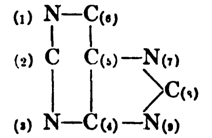
These have several distinct actions: (1) Increased irritability of the central nervous system from above downward; leading to stimulation of the psychic areas (insomnia, etc.); of the medullary centers (respiratory, vasomotor and vagus); and with large doses to heightened reflexes and tetanic convulsions. With toxic doses, the stimulation is accompanied by paralysis. (2) Increased ease of muscular contraction, progressing to loss of elasticity and to rigor; this affects all forms of muscle to a varying degree. The heart rate is thereby quickened. (3) Vasodilatation by direct action on the vessels, with moderate doses; this combines with the cardiac stimulation to quicken the circulation. (4) Diuresis results though the interaction of several factors. Caffeine is used as a psychic, muscular and respiratory stimulant; and as a cardiac tonic and diuretic. Theobromine and theophylline are relatively more effective when the peripheral actions are desired.

Members.—This group comprises the various methyl derivatives of xanthine (dioxypurine). They occur in several plants; as products of metabolism in animals; and may also be obtained synthetically. The most important are *caffeine* (trimethylxanthine), the principal alkaloid of coffee, tea, kola, guarana and maté; theobromine (3.7 dimethylxanthine), from cacao; and theophylline (1.3 dimethylxanthine), which is usually prepared synthetically. Xanthine itself, and all its other methyl derivatives, produce the principal actions of the group.

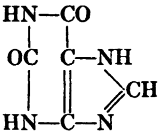
Caffeine is so feeble a base that it does not turn litmus, and the salts are dissociated by water. Its solubility is also peculiar. It was isolated from coffee in 1820 by Runge, Pelletier and Caventou, and by Robiquet. Its identity with the alkaloid of tea (sometimes called *theine*) was surmised by Berzelius and confirmed by Jobst and Mulder in 1838.

Caffeine occurs in plants of at least six families, which are scattered over many portions of the globe. These plants have nearly all been consumed by the natives as stimulants. The plants often contain volatile products or tannic acid, which slightly modify their effects. Theobromine is often associated with the caffeine; in cacao, the theobromine predominates.

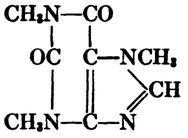
The chemical structure and derivation of the purine derivatives were elucidated by Emil Fischer. The most important are as follows:



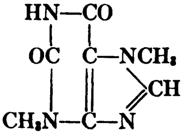
Purine (the numbers indicate the positions in which radicals may be introduced).



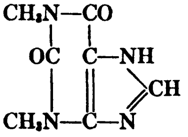
Xanthine



Caffeine



Theobromine



Theophylline

Cerebral Stimulation.—Caffeine in the form of its beverages is a popular "stimulant," tending to facilitate mental and muscular effort, diminishing drowsiness and psychic and motor fatigue, giving a sensation of comfort and cheerfulness, and relieving certain types of headache. The stimulation is apparently not followed by depression, except as it exhausts reserves. Experimental investigations indicate that moderate doses (to 0.3 Gm. in man) produce a quicker and clearer flow of thought; disappearance of fatigue; more sustained intellectual effort; more efficient appreciation of sensory impressions and more perfect association of ideas. Reaction speed is increased, especially motor, but the accuracy and delicacy of movements, particularly of acquired motor skills, is impaired, often for several days. Conditioned reflexes give precipitate reactions with a large percentage of errors, except when fatigue is relieved (Kraepelin, 1872; Hollingsworth, 1912). The central actions of theobromine are much weaker than those of caffeine (Filehne, 1886). Theophylline is intermediate. *With* *larger doses,* these effects pass into wakefulness, nervousness, excitement, tremor, palpitation and the other unpleasant reactions described under the toxicology. Still larger doses may produce delirium and temporary mania, and finally convulsions of the strychnine type. *The lower mammals* react by restlessness and excitement. The cat is said often to become frantic. Frogs do not exhibit any symptoms referable to the brain.

Hollingsworth, 1912, conducted tests on normal human subjects which led to the following conclusions: *motor speed* (tapping) is increased by small and large doses (0.06 and 0.39 Gm. of pure caffeine, respectively). With the more complicated typewriting, speed is also increased by the small dose, but retarded by the large. Errors in typewriting are fewer with all doses. *Association tests* (naming colors or opposites; calculations) are speeded by all doses. *Choice* (cancellations, etc.) seems retarded by small, and stimulated by large, doses. *Unsteadiness* (tremors) of the muscles is a frequent result. None of the stimulant effects are followed by depression. The effects start in one to three hours after oral administration and last from two to over seven hours; the mental effects are more persistent than the purely motor. The "after contraction" ("*levitation*") which occurs when resistance is removed is increased by caffeine, diminished by bromide, but little affected by barbiturate, chloral or strychnine (Sapirstein *et al.*, 1936). Caffeine causes "attacks" of rapid potential variations in the *brain action currents*. These appear identical with those produced by metrazol, cocaine and strychnine (M. H. Fischer, 1932). *Direct application of caffeine to the motor cortex* results in clonus and epileptoid convulsions similar to those caused by nicotine and strophanthin (Rizzolo, 1929).

The use of caffeine against fatigue will be discussed under the "Caffeine Beverages."

Use against Headache.—Fairly large doses of caffeine (0.5 Gm. = 7½ grains) are rather effective against certain forms of headache, such as migraine, neuralgia, fatigue, etc. The cerebrospinal fluid pressure is reported as lowered, without change of arterial pressure (W. D. Paul and Greene, 1936). The caffeine may be prescribed with acetanilid. It does not prevent the depressant effects of the latter, but rather increases its toxicity (Hale, 1909; Salant, 1912); it also increases the toxicity of alcohol and barium chloride by its circulatory action.

Use as Analeptic in Narcotic Poisoning.—Caffeine is used as an antidote against acute poisoning by morphine (Bennett, 1874); alcohol (Binz, 1878); paraldehyde (Schröder, 1887); chloral (Airila, 1913). The psychical actions are directly antagonistic, the mental and muscular coordination being immediately improved, although the effect is not lasting. The respiration (Voegtlin and Wiggers, 1918) and circulation may also be somewhat stimulated, but the effects easily become additive, so that with fatal alcohol poisoning, caffeine is actually deleterious. With morphine, the conditions are probably more favorable.

As a stimulant antidote, the caffeine is usually administered as strong, hot, black coffee, to secure the synergistic stimulant action of the heat and oils. Strongly boiled tea, through its tannin, would be a chemical antidote in poisoning by corrosive metals. Coffee has not this precipitant effect. The *mutual antagonism of alcohol and caffeine* was studied by Pilcher, 1912. He found that with the *smaller doses*, each drug tends to act qualitatively as if present alone. In alcohol sleep, small doses of caffeine cause awakening, restore the reflexes and diminish the fall of temperature. With *larger doses*, there is a qualitative change in the direction of greater depression. Light alcohol coma is intensified by moderate or large doses of caffeine; the reflexes are further depressed. With *toxic doses*, the fatality is greatly increased if both drugs are present, mainly by their deleterious action on the heart.

Spinal Cord.—Ordinary doses of caffeine heighten the reflexes (Wood, 1912; Storm van Leeuwen, 1913). Toxic doses produce convulsions of spinal origin (Bing, 1901), which agree with those of strychnine, except that the tetanus is neither as violent nor as prolonged. The exhaustion in the intervals is also less pronounced. The tetanus may produce death by fixation of the respiratory muscles. The convulsant dose is relatively large, and it is doubtful whether it has been observed in man. Ordinary toxic doses produce only tremor. The *paralytic action* of large doses can be shown in frog by protecting the muscles from rigor; *i.e.*, by ligating a leg exclusive of the nerve. Caffeine will then destroy its reflexes.

The medullary centers are moderately stimulated by caffeine. There is little or no subsequent depression, even with toxic doses. The most conspicuous effect is on the respiration. The stimulation of the vasomotor and vagus centers is interfered with by other factors, described under "Circulation."

Respiration.—In man, the respiration is scarcely affected by oral therapeutic doses (Newburgh, 1914). Cardiac dyspnea is improved by the circulatory effect. With hypodermic injection of 0.15 to 0.25 Gm., there is definite respiratory stimulation. The Cheyne-Stokes respiration of cardiovascular disease is sometimes restored almost immediately to the normal rhythm by intravenous injection of *aminophylline* (theophylline and ethylene diamine), and the effect may last for hours; 0.5 Gm. two or three times daily suffices. Theophylline in other combinations produces the same effects (M. H. Nathanson and Fitzgibbon, 1939). The respiratory stimulation by caffeine appears to be chiefly, if not entirely, central, for it occurs after denervation of the carotid sinus and aorta (Le Messurier, 1936).

The CO_2 *tension* is markedly lowered. The rate and depth of the respiration and the minute volume are increased. There is also increased gas metabolism and sometimes bronchial dilation (Higgins and Means, 1915). The respiratory response to CO_2 was not significantly altered by small or large doses in normal human subjects (Grabfield and Means, 1917).

The respiratory stimulation by aminophylline is used for the clinical *determination of circulation time,* injecting 1 cc. containing 0.24 Gm. by vein. The end point, normally in 12.4 seconds, is marked by increased depth of respiration, sometimes a gasp (Koster and Sarnoff, 1943).

Anesthetized animals respond by increased rate (Binz, 1878) and generally also increased depth of the respiration (Heinz, 1890), probably due to partial awakening from the anesthesia (Cushny, 1913). Inhibitory reflexes are less effective. *In morphinized dogs,* caffeine produces brief overventilation (two to ten minutes) with fall of alveolar CO_2; followed by normal ventilation with rise of CO_2, persisting for several hours (R. G. Smith, 1928). The respiration of *unanesthetized rabbits* may be depressed by the hypodermic injection of moderate doses, 10 mg. per Kg. (Hanzlik, 1923). *Theophylline* increases the rate and depth in chloralosed dogs and in rabbits under various narcotics. The response of normal rabbits is inconstant (Hazard and Jequier, 1938).

In respiratory paralysis by cerebral compression caffeine proved a less effective stimulant than strychnine or especially cyanide (Loevenhart *et al.,* 1918).—Breslauer-Schutz, 1921, claims useful therapeutic response from *subdural injection* in the region of the medulla.

Use in Asthma.—Prompt relief is usually obtained from intravenous injection of 0.5 Gm. of aminophylline, sometimes when epinephrine and atropine have failed. Side actions are frequent but not dangerous: vertigo, vomiting, chest pain, throbbing head (H. A. Carr, 1940). *Theophylline monoethanolamine* is effective orally with little side effects (Lamson and Bacon, 1941).

Aminophylline protects guinea pigs against the bronchial spasm of histamine and dilates excised bronchioles (R. H. Young and Gilbert, 1940; Luduena, 1942). Coffee sometimes gives relief in asthmatic attacks. The action is probably partly psychic, partly bronchial.

In guinea pigs, caffeine relaxes the bronchial spasm produced by peptone or muscarine (Pal, 1912). Bronchial dilatation is also sometimes observed in man (Higgins and Means, 1915). F. Meyer, 1915, concluded that caffeine acts mainly by stimulating the respiratory center to greater effort.

Circulation.—Caffeine acts on the heart and blood vessels, peripherally and centrally. The effects are therefore complex and vary with the dose and other conditions. The predominant action of therapeutic and moderate physiologic doses consists in vasodilatation, combined with sufficient cardiac stimulation to maintain the blood pressure, or even to raise it somewhat. Both actions combine to favor the blood flow, and would be useful in circulatory diseases; the diuretic action is a further desirable feature. On the other hand, the effects of caffeine are not as powerful or as lasting as those of digitalis, and its side actions often interfere with its use. The other methylxanthines act similarly to caffeine. Theobromine is more powerful than caffeine, and theophylline is still more active.

Intravenous injection of caffeine produces a fairly severe fall of blood pressure, with prompt recovery. The *acute fall of pressure* is presumably due to depression of the myocardium by the concentrated drug. It is not seen with other methods of administration. It is not characteristic for caffeine, but occurs as "*velocity shock*" with many other drugs. The organ volume (oncometer) falls with the pressure (indicating that the action is cardiac). Direct observation of the heart shows dilatation with diminished excursions. The heart rate is quickened and the vasomotor and respiratory centers are stimulated by the low pressure.

Stimulant Doses.—Small and moderate doses (to 20 mg. per kilogram) generally produce slight (10 to 20 mm.) rise of blood pressure, usually with more or less increase of the heart rate. The tonus of the heart is increased, and the amplitude of its excursions may be greater. This, and the faster rate, raise the output of the heart. The vein pressure is not changed (Capps and Matthews, 1913). The blood flow is increased (Landgren and Tigerstedt, 1892; Loewi, 1905). The volume of the splanchnic organs (Phillips and Bradford, 1887; Loewi, 1905) and of the cerebrum (Roy and Sherrington, 1887) increases. This oncometric change is more marked and more persistent than that of the blood pressure, and therefore indicates marked *vasodilatation.* It has been claimed that this is more powerful in the kidney than in other organs (Phillips and Bradford; Loewi), but in fact it seems to be about equal, at least in the splanchnic area (Sollmann and Pilcher). The vasodilatation is peripheral, since the perfusion method shows that the vasomotor center is actually stimulated. Decerebrate cats also show consistent stimulation of the vasomotor center (van Esweld, 1930). Ordinarily, the peripheral dilatation is more powerful than the central constriction; but under some conditions the constriction may predominate, so that the oncometer falls with the rising pressure.

The older conception of a powerful and constant constriction was based on slender and indirect evidence (mainly on the experiments of Wagner, 1885, and Schroeder, 1886). Vinci, 1895, found that caffeine gave a much larger rise of blood pressure (presumably cardiac) in animals weakened by anemia or starvation.

Depressant doses of caffeine, above 40 mg. per kilogram, progressively lower the blood pressure, until a level of 60 to 85 mm. is reached, with doses of about 140 mg. per kilogram. This level is then maintained until death approaches. The tonus of the heart is decreased, so that it gradually dilates, and the amplitude of the excursions and the output are diminished. The oncometer falls with the blood pressure, so that cardiac depression is the dominant element. It is accompanied, however, by a progressive and finally complete vasomoter paralysis, when epinephrine, splanchnic and other forms of vasomotor stimulation become less and less effective. (Epinephrine still causes a relatively small rise through cardiac stimulation.) *Death* occurs by acute cardiac failure. Caffeine serves to lower the resistance of the heart, so that the fatal dose may vary greatly in different animals.

Direct Action on Blood Vessels.—These tend to dilate when excised organs are perfused with caffeine (Cow, 1911). The effect is not great with caffeine alone, but very little caffeine suffices to counteract the constrictor effect of epinephrine (Sollmann and Pilcher). Theocin is reported to invert the constrictor action of epinephrine, ephedrine and pituitrin (R. Kohn, 1932).

Special Vessels.—The *lung vessels* are first constricted, soon ceding to dilatation (Berezin, 1914). Macht, 1914, observed dilatation of excised pulmonary artery. Theobromine was practically negative. Baehr and Pick, 1913, found no effect with caffeine on long perfusion. The *liver veins* are dilated (Berezin, 1914). The vessels on the *pia mater* and *retina* are dilated during life (Hirschfelder, 1915). The dilatation of the eye vessels may raise the intra-ocular tension even with falling systemic blood pressure (Wessely, 1915). Raphael and Stanton found no changes in the human *brain volume* (plethysmograph) after intravenous injection of 0.25 Gm. of (absolute) caffeine. (The *coronary blood flow* will be discussed after the heart.)

The Heart.—When the vagi are intact, small doses of caffeine sometimes cause slowing through stimulation of the vagus center (Ewirski, 1904) and increased vagus excitability (Fredericq, 1913). With larger doses, or always if the vagi are paralyzed, the rate is quickened. With the vagi divided, 2 mg. per kilogram increases the rate by 25 per cent; 30 to 100 mg. by 50 per cent. Beyond this there is no further increase, but the heart shows *arrythmia* and *irregularity*.

The increased rate is attributed to increased contractility of the muscle substance itself, especially in the region that sets the pace. The quickening is not due to *vagus* depression, since it occurs after atropine (Johannsen, 1869). The vagus tone is indeed lost after large doses (Aubert, 1872, and others), and the response to vagus stimulation is uncertain; but direct central vagus stimulation may still cause marked slowing. Nor is the quickening due to stimulation of the *accelerator* mechanism, for it occurs in the excised mammalian heart. Swirski, 1904, found that when the caffeine quickening had reached its maximum, a further increase would be obtained by stimulating the accelerator. (Large doses destroy the response to accelerator stimulation, Fredericq, 1913). Cushny showed that the details of the cardiac curve are different in caffeine and accelerator stimulation. Pickering, 1893, observed the quickening in embryonic chick's heart before the nervous structures become developed.

Frog's Heart.—Small doses increase the rate (Voit, 1860), excursions (Wagner, 1885), pulse volume, and especially the absolute force (Dreser, 1887). The diastole is shortened more than the systole. The refractory phase is not changed (K. Junkmann, 1925). Large doses cause slowing and weakening (Maki), with diastolic tendency (Faval). The heart beats for some time after the skeletal muscles are in rigor (Wagner). The final arrest may be either in systole (Johannsen, 1869) or diastole (Faval). When perfused in Ringer's solution, 0.025 to 0.2 per cent increases the amplitude, 0.2 to 2 per cent decreases the amplitude and produces irregularities of rhythm and automaticity (Cheney, 1935). The *terrapin's* heart responds like the frog's (Beyer, 1885). Low concentrations of caffeine, theobromine and theophylline increase the response of the turtle heart to vagus inhibition; high concentrations inhibit the response. All concentrations potentiate acetylcholine (A. Lamalle, 1941). *Perfusion of the medulla in turtles* with 0.04 per cent of caffeine has practically no effect on the heart rate, in contrast with strychnine (A. D. Bush, 1919).

In *excised and perfused mammalian heart*, caffeine and the other xanthines produce increased rate, amplitude and force of the cardiac contraction, and generally quickened coronary flow (Hedbom, 1899). The increased amplitude is first in the systole, then also in the diastole; the cardiac tonus is not increased (Plavec, 1909). The stimulation is greatest with theophylline, then theobromine, then caffeine. These experiments seem to refer only to stimulant concentrations, and they may be considerably modified by changing conditions (Lifschitz, 1907; Plavec, 1909). *Electrocardiograms from the excised mammalian heart* show that while the three principal methylxanthines agree in quickening the rate, they differ in their effects on conduction. This is depressed by theobromine, increased by caffeine and theophylline (Sakai, 1919). *Excised papillary muscle* of cats is not affected by ordinary concentrations of the methylxanthines; high concentrations, 1:5000 to 1:1000, produce brief increase of systolic tension (S. Krop, 1944).

Mammalian Heart in Situ.—The effects of the various doses were studied by Pilcher, 1912, with the results described under the general discussion of the circulatory effects.

Experimental Heart Block.—In complete block, caffeine increases the strength of the ventricular contraction. Larger doses produce ventricular extrasystoles and tachycardia. The strength of the auricles is temporarily quickened (Egmond, 1913).

Coronary Circulation.—Earlier investigators generally reported considerable increase of coronary blood flow in perfused hearts (Heathcote, 1920, bibliography; Bodo, 1928), greatest with theobromine salts, then theophylline ethylene diamine, then theophylline sodium acetate, and least with caffeine (Gilbert and Fenn, 1929). This has been interpreted as dilatation of the coronary vessels; but in the beating heart, the coronary flow is influenced not only by the tonus of the coronary vessels, but by the cardiac contractions; and in the living animals also by the aortic blood pressure (F. Meyer, 1912). In experimental animals, the increased flow does not precede but follows the myocardial stimulation (N. H. Boyer, 1943). However, dilatation plays a part at least, for caffeine and aminophylline increase the coronary flow in perfused nonbeating (fibrillating) heart (L. N. Katz and Lindner, 1939). Boyer, Wégria and Green, 1941, report some increase of coronary flow from intravenous and intracoronary injection of aminophylline in dogs. The coronary dilatation was confirmed by Lindner and Katz, 1941. Prolonged administration of aminophylline to dogs with experimental myocardial infarction reduces the size of the infarct by developing anastomoses, but it is less effective than papaverine (Mokotoff and Katz, 1945).

The circulatory effects in man correspond with what would be expected from animal experiments. With doses to 1.5 Gm. of caffeine the acute effects are inconstant and generally slight. The heart rate may be slowed, quickened or unchanged (literature, Sollmann and Pilcher). Palpitation is common, but apparently largely subjective. The blood pressure may rise (Wood, 1913); or fall (Mirano, 1906); or remain unchanged (Lucas, 1914; Newburgh, 1914). The volume of the human arm is diminished (Hewlett, 1913). The blood flow tends to improve by increased systolic output. Intravenous injection of 0.48 Gm. of aminophylline is reported to increase the cardiac output and to produce brief vasodilatation in the skin (H. J. Stewart and Jack, 1940).

A. Grollman, 1930, found that caffeine citrate in doses smaller than 0.5 Gm. had no effect on cardiac functions. With 0.5 to 1 Gm., there was generally a slight increase of cardiac output, slight or no change in the pulse rate, increase in the oxygen differential between arterial and venous blood and generally 10 to 30 per cent increase of oxygen consumption. When the caffeine caused marked subjective nervous effects, there resulted more marked increase of cardiac output, blood pressure and pulse rate and no rise in the arterial : venous oxygen differential. Hypodermic doses of 0.3 to 0.5 Gm. in resting men produce a definite increase of the total *blood flow* (Krogh-Lindhard method). The improvement occurs by increased systolic output. It does not occur during work. Means and Newburgh, 1915, attribute the rest effect to increased venous return to the heart, by some action outside the heart. During work, the venous return is adequate, even without caffeine, and is not materially increased by the drug. In advanced *myocarditis*, full and continued doses of caffeine (about 1 Gm. per day) cause a progressive and permanent lowering of blood pressure, reaching a total of 10 to 50 mm. This is parallel to the diuresis and to the relief of the edema and other symptoms (L. Taylor, 1914). Theobromine does not lower the pressure, although it is otherwise equally or more efficient.

Therapeutic Effects on Circulation.—The methylxanthines are used as cardiac stimulants in syncope, and especially in cardiac dropsies. They lack the permanent, tonic action of digitalis, but are useful as adjuvants or when a quick effect is desired. Theobromine deserves preference over caffeine. It is effective on the first day, if at all. The side actions of caffeine interfere with its employment, especially in excitable patients. In hypotension and infectious diseases, caffeine fails to improve the circulation (Newburgh, 1914; Lucas, 1914). Aminophylline does not affect improvement in peripheral vascular disease, nor does it reduce the pressure in hypertension (review, Boyer, 1943). Intravenous injections sometimes cause sudden death (G. A. Merrill, 1943).

Theobromine and theophylline (aminophylline) in angina pectoris were introduced (by Askanazy, 1895) with the object of increasing the coronary blood flow; and diethylene diamine was added to theophylline to enhance the dilatation. It has little effect, however, except to increase the solubility of the theophylline (K. H. Osterwald and Meurer, 1939). The earlier clinical reports indicated relief of cardiac pain in angina, coronary thrombosis and sclerosis; however, when methylxanthines were compared with placebos, extensive series failed to show any such effect (Evans and Hoyle, 1933; H. Gold *et al.*, 1937). Other observers report that the tolerance of some angina patients for standardized work is increased, for some twenty minutes with intravenous, longer with oral administration. Theobromine sodium acetate (0.5 Gm., four times per day) was as effective as theophylline sodium acetate (0.15 Gm., four times per day) and more economical; aminophylline was less effective; caffeine had little value (M. G. Brown and Riseman, 1937; R. L. Levy *et al.*, 1940; G. V. Le Roy, 1941). Aminophylline relieves coronary spasm from pituitrin injection in animals (P. J. Hanzlik and Moy, 1945).

The dyspnea and Cheyne-Stokes respiration of cardiac failure is often promptly improved by aminophylline (R. Singer, 1927), but no more than by theophylline or theobromine. The improvement is parallel to the decrease of venous and intrathecal pressure, and is perhaps aided by relaxation of bronchiolar spasm (J. A. Greene *et al.*, 1937). The pressure of the *cerebrospinal fluid* may be lowered without change of arterial pressure (W. D. Paul and Greene, 1936). A. Blau, 1936, reports that the fall after 0.35 Gm. of caffeine, clinically, is transient.

Pruritus in various dermatoses is reported to be relieved immediately by aminophylline, especially with intravenous injection (E. Epstein, 1946).

Effects on the Urine.—The most important therapeutic effect of caffeine consists in a considerable diuresis, but the methylxanthines have been largely displaced by the more potent mercurial diuretics. The increase concerns mainly the water of the urine. The absolute quantity of all urinary solids is also increased, but less than the water, so that their percentage is lowered. The efficiency varies with conditions, especially with the amount of water in the body (Widmer, 1914); the diuresis is most abundant in dropsical conditions, and fails entirely with dry food. It is much greater in man and in wet-fed rabbits than in dogs. Cats practically do not respond. It fails also in glomerular nephritis, but is effective in tubular nephritis unless the vessels are involved. The albumin in nephritis may be increased. Theobromine and especially theophylline are more effective. This difference is explained in part by the relatively larger doses which can be taken without prohibitive side actions. *The mechanism of the diuretic action of the methylxanthines* is chiefly, if not solely, that of increased glomerular filtration through increased blood flow and rise of glomerular capillary pressure, due to local vascular adjustments within the kidney (Phillips and Bradford). There is no evidence that reabsorption from the tubules is diminished (as suggested by Sobieranski), and it is improbable that changes in the water affinity of the tissues are involved.

Historical.—The scientific investigation of the diuretic action of the methylxanthines started essentially with von Schroeder in 1886 and 1887. He found that the increased urine flow is not conditioned on increase of the general blood pressure, and therefore concluded that it could not be due to increased "filtration," in the sense of the Ludwig theory, which he conceived to demand increased blood pressure. He therefore assumed that caffeine must directly stimulate the "vital" secretory function of the renal epithelium, according to the Heidenhain theory. The fundamental error of von Schroeder consisted in the assumption that the general blood pressure is an index of the filtration pressure in the glomeruli, without considering the probability of vasomotor adjustments within the kidney, or of an altered balance between general vascular tone and cardiac output. These conditions would be reflected in the kidney volume much more closely than in the general blood pressure; and in fact, Phillips and Bradford, 1887, and others since then, observed that the caffeine diuresis is paralleled fairly closely by increase of the kidney volume, although the agreement is not absolute. The methylxanthines cause a larger change of renal volume than other diuretics, and the dilatation lasts for two hours after intravenous injection of caffeine or theobromine (W. E. Read). Increased kidney volume implies increased filtration pressure, unless it is due to contraction of the veins; the latter was excluded by the observation of Loewi, 1905, that caffeine increases the renal blood flow. Sollmann and Pilcher, 1911, showed that caffeine produces considerable dilatation of the renal vessels if these have been previously constricted by epinephrine, while at the same time the output of the heart is increased. The renal blood flow is increased (in rabbits) even by nondiuretic doses of caffeine (Kihara, 1928). The vasodilator action is directly on the renal vessels, for it occurs in eviscerated rabbits with automatic blood pressure compensation (Ozaki, 1927). Richards and Schmidt also showed marked dilatation and increase in the functioning glomeruli by direct microscopic observation in the frog. The correspondence between the vascular changes and urine flow is not perfect (Cushny and Lambie, 1921), but some divergence might be expected in an organ of such complicated vascular topography.

Interference by Vasoconstriction.—While the stimulation of the vasomotor center has not ordinarily the importance attributed to it by von Schroeder, it may sometimes be sufficiently powerful to overcome the peripheral dilator effect. At all events, the diuresis is aided by the hydrocarbon narcotics. Curare is also said to aid the diuresis (Cervello and LoMonaco).

Denervated Kidney.—Excised and re-implanted kidney, after resumption of its normal function, responds in the normal manner (oncometer and diuresis) to theobromine and caffeine; also to urea and hypertonic saline (Quinby, 1917).

Perfusion of Excised Mammalian Kidney.—Varying results have been described (*cf.* Sollmann and Hatcher, 1907); but when positive, the effects were generally in the direction of increased vein flow and ureter flow, pointing to vasodilatation. Richards and Plant, 1915, also obtained increased ureter flow when the perfusion flow was kept constant. This has been interpreted as showing a noncirculatory factor in the diuresis; but it is doubtful whether changes in the renal circulation are excluded in this manner. *Heart-lung-kidney preparations* of dogs, perfused at constant pressure, also respond to caffeine by increased vein and urine flow. The chloride concentration in the urine increases, that of urea decreases, but the total quantity of urea increases. These changes in composition agree closely with those that occur in equal diuresis produced by rise of perfusion pressure; indicating that the changes of composition are secondary to the diuresis (Verney and Winton, 1930).

Ureter Peristalsis.—Lucas, 1907, found that caffeine has a tonic effect on the pelvic portion of the ureter.

The creatinine clearance test (Rehberg) has given results indicating increased glomerular filtration with normal tubular reabsorption (Schmidt and Leitle, 1932; Hermann *et al.*, 1933); Blumgart *et al.*, 1934, failed to demonstrate this.

Water-Affinity of Blood and Tissues.—Paul Spiro, 1918, reported that caffeine causes the blood to lose fluid even if the kidneys had been previously removed, and it was argued from this that it diminishes the affinity of the serum colloids for water and salts, and thus liberates fluid for filtration by the lymph or urine (Karl Spiro, 1920). This seemed supported by the observation of Ellinger *et al.*, 1921, that serum perfused through frog legs produced edema more readily if caffeine (1:7000) was added. However, caffeine increases the acidity of muscles, and this may account for their increased water affinity. They also reported increase in the speed of *ultrafiltration* of serum through colloidal membranes when caffeine was added, even in the dilution of 1:56,000; increased swelling of colloidal gels when placed in such serum, and aggregation of the serum colloids, observable with the ultramicroscope. Analogous results were reported by Brühl, 1929, and Szeloczey, 1929; while others obtained contradictory results (Faludi, 1928). The significance is doubtful. *The imbibition affinity of the whole frog* (*i. e.*, the quantity of water taken up on immersion, the reciprocal of the quantity lost in dry air, by winter frogs) was not increased by caffeine, although mercurials and urea increased the water retention (Molitor and Pick, 1922)

The water and salt content of the blood have been reported as diminished and as increased. The divergence is explained partly by the water and salt content of the body, but especially by the stage of the diuresis. Generally, the proportion of water and chloride in the blood diminishes during the diuretic stage, and rises to the normal during the compensating oliguria (Paul Spiro, 1918; clinically, Veil, 1922). Patients with congestive heart failure respond to aminophylline by considerable *increase of plasma volume*, persisting after the diuresis, although it may eventually fall below the control level (Calvin *et al.*, 1940).

The Chloride Level of the Blood and Urine.—In rabbits, the caffeine group may increase the plasma chlorides, without increasing the quantity of the urine (Katsuyma, 1898); in man, the chloride concentration is generally diminished (Sellei, 1912; Wuescher, 1925), and only rarely increased (for instance in diabetes, E. Meyer, 1905; drop of plasma chloride in nephritis, E. H. Mason, 1918). With rabbits, the caffeine group maintains or restores a high chloride excretion when this has been lowered by deficient salt income or by sulfate or water diuresis (Barcroft and Straub, 1910); but in dog, and in man, the chloride retention is not broken down (Sollmann and Hofmann, 1905; Saccone, 1911). Neither aminophylline nor salyrgan nor merbaphen produces a significant change in the chloride level of the human blood (Hansen *et al.*, 1931). *Bromide excretion* is accelerated in rabbits (Frey, 1910).

Source of the Chloride and Water Excretion in Rabbits.—Sasaki, 1925, found that continued administration of theobromine increased the water excretion only when the rabbits are fed on wet food; but that the chloride excretion is increased also on dry food, *i. e.*, independently of the diuresis. Analysis of the tissues shows that the water excreted in excess of the income is derived mainly from the skin; the chloride from the skin and muscles. Eventually the chloride level of the blood is also lowered.

Other Constituents of the Urine.—Increased urine flow generally lowers the concentration of urinary solids, but increases the absolute quantity, at least for a time. This holds true also of caffeine (von Schroeder, 1886). The relative increase of the different solids is not the same (salts and urea, Le Noir and Camus, 1903; Na and K, Bock, 1911; sulfate and phosphate, man, Wuescher, 1925). The phosphate concentration of the blood and urine is lowered, proportional to the diuretic efficiency of the xanthine derivatives (Bollinger, 1928). *The urea clearance test* in nephritic and hypertensive patients was not affected by caffeine, theobromine or salyrgan (I. H. Page, 1933). Caffeine, in common with other diuretics, increases the amount of benzoate that can be synthesized into *hippuric acid* (Astolfani, 1905). *Purine*, intravenously or by mouth, increases the *uric acid* clearance by more than half (Bröchner-Mortensen, 1939).

Theories of Direct Cellular Action.—The diuretic action of the caffeine group has also been attributed to direct effects on the renal cells; either to stimulation of secretion (von Schroeder), or to paralysis of reabsorption (Sobieranski), or to alterations in the glomerular filtering membrane (Cushny and Lambic). These assumptions, which are practically unsupported by positive evidence, were based essentially on the inadequacy of the earlier attempts at the more mechanical explanations. The advances that have been made may dispense with them. On the other hand, the mechanical factors can not be effective if the renal cells are too greatly altered.

Sobieranski, 1903, attributed caffeine diuresis to *diminished reabsorption* of the glomerular filtrate. His arguments were based on observations on the excretion of stains, the interpretation of which is unconvincing. Similar objections hold against the conclusions of Hirokawa, 1908, based on the osmotic pressure of the renal cortex; and against those of Greenwald, 1907, on the chloride of the cortex.

Oxygen Consumption.—Barcroft and Straub (1910) reported that caffeine produced increased oxygen consumption in the kidneys—evidence of local energy consumption that would not be needed by a physical filtration process. Other observers have failed to obtain this effect (Richards and Schmidt; Kihara, 1928); and on the other hand, the oxygen consumption of the kidney may be increased by increasing the arterial pressure (Fee and Hemingway, 1928). Indeed, there is no constant parallelism between the urine output and the oxygen consumption, in intact or excised kidneys (Van Slyke, Rhoads *et al.*, 1934). Anuria by nephrotoxic poisons may exist with increase or decrease of renal oxygen consumption (Chuta).

The *aglomerular kidney* of the toadfish does not respond to caffeine and theophylline by diuresis, but by oliguria (Bieter).

The Influence of Conditions on the Diuretic Response.—The improvement of glomerular filtration is influenced by the amount of filterable water, by the permeability of the glomerular filter, and by the patency of the renal tubules.

Excess of Fluid.—Superabundance of fluid is evident in edemas and ascites; and these conditions therefore give the largest response to the caffeine diuretics (Hofmann, 1890), provided that the conditions that caused the edemas are no longer operative. A part of the diuretic effect in cardiac edemas, however, is due to the cardiac improvement. In normal subjects, a fairly liberal water supply is necessary for continued diuresis (Sobieranski, 1895; Loewi, 1905); however, the free diuresis produced by a liberal supply of fluid is not further enhanced by caffeine (Sollmann and Hofmann, 1905; diabetes mellitus, Meyer, 1905).

Reduction of fluid interferes notably with caffeine diuresis, and is the chief reason why the large initial diuresis can not be maintained (clinically, Le Noir and Camus, 1903; animals, Phillips and Bradford, 1887; M. H. Rees, 1924), for in the proportion that the initial diuresis removes the excess of fluid, the caffeine finds it more difficult to obtain further fluid. Hemorrahge (Michaud, 1904), muscular work (perspiration) (Wuescher, 1925) and restricted consumption of liquids similarly diminish or prevent diuresis.

Habitual use of coffee or tea also confers some diuretic tolerance, so that two or three times more of caffeine, theobromine or theophylline are required to produce diuresis than when the same individual is abstinent for two months (Eddy and Downs, 1928). This habituation tolerance has also been observed in animals (H. B. Myers, 1918; Kihara, 1928).

Interference by Renal Irritation.—All forms of nephritis are likely to interfere with the diuretic response. Experimentally, the interference is greatest in glomerular and least in purely tubular nephritis.

Caffeine in Experimental Nephritis.—Hellin and Spiro, 1897, found caffeine ineffective in glomerular and general nephritis, but quite effective in pure tubular nephritis. This has been confirmed by Schlayer and Hedinger, 1907, and by Pearce, Hill and Eisenbrey, 1910. The failure of diuresis is accompanied by failure of the oncometric reaction. In *uranium nephritis*, diuretics, including caffeine, are effective during the early polyuric stage; but they become ineffective when the anuric stage is reached, although the circulatory response may be well preserved. This depends on the intactness of the renal epithelium (MacNider, 1914). In the subacutely fatal form, caffeine and the other methylxanthines did not prolong life (Christian, 1914). For *chronic nephritis*, on the other hand, theobromine and theocine were distinctly harmful, since they diminished the phthalein output and the animals died more promptly (O'Hare, 1915), although the nitrogen excretion was unchanged and the elimination of urine and chloride was increased (Fitz, 1914). Finally, the kidneys ceased to react. This is especially marked if the caffeine has been preceded by several injections of saline (Mosenthal and Schlayer, 1913).

Renal Irritation by the Caffeine Group.—Ordinary doses of caffeine do not appear to produce demonstrable injury, even in nephritic subjects. Large doses may increase the albuminuria. With theophylline the continued use even of moderate doses is considered inadvisable.

Sollmann and McComb, 1899, found that caffeine did not increase a physiologic albuminuria, and Emerson, 1903, saw no increase of albumin in acute or chronic nephritis under theobromine. Pouchet and Chevalier, 1903, claim that large doses of theophylline injure the glomerular and tubular epithelium. Animals respond to large doses of caffeine (40 mg. per kilogram), especially when long continued, by definite nephritic changes: albuminuria of 1.4 per 1000; leukocytes, epithelium and casts in the urine. The kidneys show dilated vessels, cloudy swelling, to vacuolar degeneration and necrosis of the epithelium, and slight interstitial swelling. These histologic changes may be present even when the urine appears normal. The lesions are usually transitory, disappearing a few days after discontinuance. No lesions are perceptible with doses of 5 to 10 mg. per kilogram, corresponding to 5 to 10 grains in man (Vinci, 1914).

Phenylalanine and tyrosine inhibit purine diuresis if they are injected into the peritoneum; the tyrosine by producing severe liver damage (Shambaugh, 1927).

Relative Potency of Xanthine Derivatives.—Caffeine has been largely supplanted as a diuretic by theobromine and theophylline, which are credited with a much more powerful action. With theobromine this is largely because the customary dose is four times that of caffeine; with theophylline, the superiority is genuine. For equal diuretic effect, the dosage of caffeine is to that of theobromine and theophylline as 1:1.2:0.4 (Eddy and Downs, 1928). Theophylline may be effective when theobromine fails completely (W. Goldring, 1929). Both produce less of the nervous side actions than caffeine. The drugs of the caffeine group are often administered as *double salts*, with sodium acetate, benzoate, salicylate, etc. This increases their solubility, but does not otherwise alter their actions.

Mendel and Kahn, 1913, found that most of the other methylated xanthines are not diuretic. 1:7:9 *trimethyl 2:8 dioxypurine* (Johns) was examined by Salant and Connet, 1918. It is a weak cardiac stimulant, little, if at all, diuretic for rabbits, and much less toxic than caffeine. *Tetramethylxanthine* (1.3.7.9) is reported to have much less muscular and tetanic potency than caffeine (Paderi, 1928 .

Therapeutic Use of Diuretic Action.—The methylxanthines are employed mainly for the removal of *cardiac effusions*, to supplement digitalis and mercurials. The diuresis is proportional to the effusion, sets in promptly and ceases when the drug is withdrawn. It is therefore especially useful for two or three days at the beginning of the most slowly acting but more permanent digitalis treatment. *Caffeine* is the least active of the series. It may be given in the doses of 0.3 Gm. (5 grains) of citrated caffeine, in watery solutions, three times a day, but Taylor found at least 0.5 Gm., four times daily, necessary for a full effect. *Theobromine* (1 Gm. or 15 grains of theobromine-sodium-salicylate in water, four times a day) has the advantage of producing a better diuretic response with the least side actions. It has also been used intravenously, 20 cc. of 5 per cent, Neuhof, 1913; but it is doubtful whether this is justified. *Theophylline* (theophylline-sodium-acetate, or theocin) is the most powerful, but has been charged with sometimes causing renal irritation. Its dose is 0.3 Gm. = 5 grains, three times per day, administered in hot tea. The xanthine diuretics are also useful in *hepatic effusions*. In *renal* effusions, their effect is less certain. In acute or chronic parenchymatous nephritis, there is often no response whatever, while chronic interstitial nephritis usually responds (J. Miller, 1912); but unless the dosage is very small and carefully watched, the toxic side actions may set in, and the renal condition grow worse. It would therefore be better to avoid the methylxanthines when the kidneys are acutely irritated. In anuria, the methylxanthines are generally ineffective. Christian *et al.*, 1915 and 1916, state that diuretics are generally ineffective in chronic nephritis, unless there is edema. They would therefore be of little use against nephritic toxemia.

Skeletal Muscle.—Ordinary doses of caffeine increase the functional activity of skeletal muscle so that it contracts more readily and more completely and powerfully, and is less easily fatigued (Wood, 1912). This improvement is at least in part peripheral, for it can be seen in excised or curarized frog's muscle. The relief of ordinary *fatigue*, however, is central, for ordinary muscular fatigue is itself central. Larger doses of caffeine produce gradual progressive *contracture*, with considerable tension and decreasing response to extraneous stimuli. This culminates in irreversible rigor with histologic coagulation changes, even in living animals. All the stages are accompanied by increased production of lactic acid, which is oxidized if the oxygen supply is adequate; otherwise it accumulates and contributes to the rigor. The addition of caffeine to unstimulated excised frog muscle increases its *oxygen consumption* by four to twenty-four times (Saslow, 1937). The oxygen consumption of *nerves* is increased by concentrations below 0.5 per cent and diminished by stronger solutions (Sherit, 1930).

The Stimulant Phase of Caffeine.—Smaller stimuli suffice to produce contraction (Paschkis and Pal, 1886). The latent period is shortened. The height and rapidity of the contraction are greater and a larger weight can be lifted (Kobert, 1881). Fatigue is lessened and a greater amount of work can be performed (Dreser, 1890), if the load and stimulation are optimal; but with excessive load or stimulation, caffeine diminishes the total work. The other methylxanthines affect muscle qualitatively like caffeine (Golowinsky, 1915).

The Depressant Phase.—As the dose or concentration is increased, these effects are reversed. The contraction becomes less powerful and the curve resembles that of a fatigued muscle: *i. e.*, it is lower and more drawn out. This lengthening shows first in the relaxation (Buchheim and Eisenmenger), eventually also in the contraction. The elasticity is lessened. The muscle is exhausted more rapidly by tetanus. Similar muscular effects are produced by xanthine (Paschkis) and creatine (Dreser)

Caffeine rigor was observed by Voit, 1866, and then investigated by Johannsen, and by Schmiedeberg, 1872. Its occurrence in the living body can be demonstrated by hypodermic injection in certain species of frog (the European Rana temporaria, and the ordinary American laboratory frog, R. pipiens); while another European frog (R. esculenta) is less susceptible to the rigor and succumbs to spinal convulsions. The heart may continue to beat strongly for some time. Mammals also show some stiffness after large doses of caffeine, but actual rigor results only if the alkaloid is injected directly into an artery. The coagulant action is possessed by other xanthines, being strongest with xanthine itself and progressively weaker with theobromine, theophylline and caffeine (Filehne, 1886; Dreser). The muscle in caffeine rigor is inexcitable and appears white, bloodless, stiff and considerably swollen and shortened, and is acid to litmus (Ransom, 1911). Perfusion of the muscle with saline or blood, if undertaken soon after the onset of the rigor, restores the plasticity but not the excitability (von Fürth). *Local anesthetics* tend to diminish the production of rigor, but this is attributed to a purely physical effect on the distribution coefficient (Schneller, Zips).

Microscopic Changes.—If caffeine is applied to a teased muscle under the microscope, the contents of the fiber are seen to move; the cross striations disappear and the longitudinal striae become more prominent. The sarcolemma becomes detached. The fibers shorten by half (Johannsen). These changes have been studied by Secher, 1914, through perfusion with dilute solutions of xanthine and the various methylxanthines, which all produce similar effects. The histologic changes increase with the concentration, to disorganization (caffeine, 1:2000). Short of disorganization, the changes are reversible. The disorganized fibers also eventually regenerate, provided their nuclei are intact. Similar changes are produced by chloroform and other poisons. Mammals require higher concentrations (Cheney, 1939).

Nature of Caffeine Contracture.—The spontaneous progressive contraction of muscle by caffeine is associated with the production of lactic acid (Ransom, 1911), a large consumption of oxygen (Meyerhof, 1921), and the production of heat; the total heat production corresponding closely with that of exhaustion by artificial stimulation (Hartree and Hill, 1924).

Coagulation of Muscle Extracts.—Rigor may be produced in living animals by the injection of a number of other substances in sufficient concentration; for instance, by chloroform. All of these, as well as caffeine, favor the coagulation of muscle extracts (von Fürth, 1896). However, certain substances coagulate muscle extracts even more actively, but are incapable of producing rigor during life.

Muscular Effects in Man.—Hyde, Root and Curl, 1917, in fasting subjects, found considerable increase of muscle power and endurance after 0.09 to 0.15 Gm. of caffeine, but marked depression after 0.23 Gm. (by mouth, as beverage). The increase of efficiency is due partly to a lesser feeling of fatigue (Rivers and Weber), but it is at least in part peripheral, since the efficiency is also increased when the muscle itself is stimulated electrically.

Creatine.—Caffeine increases the creatine content of the muscles even after curare. Riesser, 1916, attributes the effect to increase of the sympathetic muscular tone.

Smooth Muscle.—The effect of caffeine on smooth muscle consists in a longer and more persistent contraction curve. Larger doses prolong the period of relaxation. The tone seems to be affected differently in various muscles. The *arteries* are relaxed by relatively small doses; whereas the caffeine has a tonic effect on the pelvic portion of the *ureter* (Lucas, 1907). It has little effect on the uterus (Röhrig). *Biliary colic* is sometimes promptly relieved by slow intravenous injection of 0.25 to 0.5 Gm. of aminophylline (Butsch *et al.*, 1936; Gladstone and Goodman, 1944).

Intestines.—Caffeine has little or no effect on normal peristalsis (Nasse, 1866); but indirect contact with *excised intestine* modifies the functions. Salant and Schwartze, 1916, state that the contractions are stimulated by dilute solutions (caffeine, 1:10,000; theobromine, 1:25,000; theophylline, 1:50,000). Higher concentrations (1:2000) produce marked depression of the rhythm and tonus. The movements of the excised *stomach of frogs* are paralyzed by dilutions of 1:2000 to 1:100,000 (Agnoli, 1930).

Sympathetic System.—Fredericq and Melon, 1922, found that caffeine, theobromine and theophylline destroy the response of the heart to accelerator stimulation. They attribute this to paralysis of the accelerator endings. They also point out the *mutual antagonism between caffeine and epinephrine* in the arteries and intestines; *i.e.*, after epinephrine, caffeine dilates arteries and contracts the intestinal muscle.

Digestion.—In man, 80 to 250 mg. of caffeine stimulate acid gastric secretion, copiously with the larger dose. The stimulation is synergistic with that of alcohol and histamine. Large doses may produce nausea. Continued use of excessive quantities tends to functional hyperchlorhydria, probably indirectly through nervousness.

Similar and even greater stimulation is produced in cats by intravenous or oral administration. It occurs after atropine, and is therefore probably directly on the parietal cells, without excluding the possibilty of an additional central action (J. A. Roth and Ivy, 1945). Alternation of caffeine and histamine results in hemorrhagic erosions and "peptic ulcers" of the mucosa. Dogs do not show the increased gastric secretion (J. A. Roth and Ivy, 1944). Caffeine alone does not produce peptic ulcers in cats or rats, even when large amounts are administered daily for weeks, unless fatal doses are injected intramuscularly (G. Giddings *et al.*, 1945). In man, pepsin secretion is only mildly stimulated by pepsin or histamine. The two together are more effective than simple summation (M. I. Grossman *et al.*, 1945).

Other Peripheral Actions.—Caffeine has no action on peripheral nervous structures when it is used systemically (Aubert, 1872); nor does it cause any local irritation.

It has a paralyzing action only when it is applied in a very strong paste directly to the nerve (Pratt). It does not act on any *ganglia* or on any *glands* other than the kidney; nor on red corpuscles, nor on fibrin formation. Small doses increase the movements of leukocytes in shed blood, while higher concentrations kill them. Arkin, 1913, found *phagocytosis* unaffected, *in vitro*. *Hyperthrombinemia* is induced in dogs and other animals by single oral doses of caffeine, theobromine and theophylline, not by other purines or pyrimidines. It persists for several days and may be continued by repeated administration (J. B. Field *et al.*, 1944). *Blood coagulation* is prevented by the addition of 2.6 per cent of caffeine and sodium benzoate, even when calcium chloride is added. Caffeine changes the coagulability of the *euglobulin* and appears to be adsorbed by this fraction. It suppresses the complement of the serum (Klinka, 1929). *Milk secretion* is not affected by caffeine (Ott and Scott, 1912). The actions of caffeine on *lower organisms* are not characteristic (Brunton, 1882: oxidation of guaiac; Haskins, 1903: gas formation by yeast; Bokorny, 1894, and Korentschewsky, 1903: amebae; Romanes, 1867: medusae; Sollmann, 1906: adult and embyronic fish; Pickering, 1893: embryonic chick's heart; Ransom, 1912: germination of seeds). Concentrations of 0.1 per cent and higher depress the oxygen consumption of fertilized *ova of sea urchin;* 0.2 per cent and higher decrease the cleavage rate (R. H. Cheney, 1945). Caffeine (and less markedly, strychnine and atropine) changes the *heliotropism* of the fresh-water crustacean Diaptomus, which is naturally neutral to light, to intensely negative; this is changed to positive by carbon dioxide (A. R. Moore, 1913).

Metabolism.—The results of different investigators have been contradictory, but it appears that caffeine causes a rather small and variable increase in urea and CO_2. Both effects are probably indirect; the urea is explained by the diuresis, the CO_2 by the increased movements. This also accounts for the slight rise of temperature.

Basal Metabolism.—Means, Aub and DuBois, 1917, found in man a constant increase (7 to 23 per cent) of *basal metabolism* from doses of 0.5 to 0.65 Gm., the maximum occurring in one to three hours. The respiratory quotient was not changed. The elimination of *water* from the lungs and skin was increased. The *total nitrogen* of the urine was also increased by 6 to 37 per cent. The *pulse rate* showed no significant changes. Smaller doses do not influence basal metabolism (3 to 6 mg. per Kg., Haldi *et al.*, 1941). *Large doses of caffeine* increase the basal metabolism of guinea pigs by 40 to 75 per cent (Womack and Cole, 1934). In rats, caffeine increases the basal metabolism, but decreases the total metabolism (Chahovitch and Vichnjitch, 1928). Caffeine is reported to increase the oxygen consumption of rats in winter and spring, but to decrease it in summer and autumn. With rabbits it is increased in summer (Hindesmith and Angstenberger, 1939). C. J. Lehmann, Voit, Roux and others demonstrated increased urea excretion after caffeine; Reichert, increased heat production; Salant and Rieger, 1914, found slight changes in the excretion of creatine and creatinine.

Blood Nitrogen.—Laufberger, 1923, reported increased creatine, creatinine and calcium; no increase of uric acid or residual nitrogen.

Temperature rise was demonstrated by Binz and Peretti, 1878. It is slight in normal animals (1° to 1.5° C.). It is perhaps rather more effective in preventing the fall of temperature which occurs in light narcosis, but is ineffective in deep narcosis (Pilcher, 1912). The rise is much greater in thyroidectomized dogs (Karelkin, 1914).

Glycosuria.—During caffeine or theobromine diuresis, there is commonly a slight hyperglycemia and glycosuria, especially in rabbits fed on carbohydrate food. However, it occurs also in fasting animals (E. Hirsch, 1915). It may be induced by oral administration, also in cats, but not in dogs (Salant and Knight, 1909). The phenomenon, which is seen also with other diuretics, has not received a satisfactory explanation (Miculicich, 1912). It is not renal, for sugar appears in the urine only when there is a considerable rise of blood sugar (Hirsch). The hyperglycemia indicates increased glycogenolysis, which resembles that produced by piqûre (Nishi, 1909). Like this, it is generally (but not always; Jarisch, 1914) prevented by section of the splanchnics or excision of the suprarenals (A. Mayer, 1906) and by nicotine (Hirayama, 1911). It must therefore be usually central, perhaps through increased reflex irritability.

Absorption, Fate and Excretion.—Caffeine is readily and completely absorbed: none appears in the feces even after large doses. Only a small fraction is excreted unchanged in the urine. This excretion starts and is mainly completed promptly, but traces may continue for two or three days (Salant and Rieger, 1912). A somewhat larger fraction loses a part of its methyl group, and appears in the urine as di- and mono-methylxanthines, and with caffeine and theophylline as partly methylated uric acids. The excretion of true uric acid is not increased in man (O. H. Buchanan *et al.*, 1945). It is not known whether this is effected by oxidation or hydrolysis. The remainder—up to 80 per cent—is oxidized to urea. Theobromine does not produce this increase (V. C. Myers and Wardell, 1928); and a larger fraction (32 per cent) escapes decomposition. The greater part leaves as heteroxanthine.

Quantitative Excretion.—The quantity of caffeine which is extracted unchanged varies with the dose and with different animals: only 1 per cent in carnivora, less than 8 per cent in man and 6 to 20 per cent in rabbits (Rost, 1895; Salat and Rieger, 1912). The relative quantity of the various mono- and di- methyl-xanthines also varies in different animals, representing 10 to 40 per cent of the caffeine (Albanese, 1895). The demethylation is retarded by alcohol (Salant and Phelps, 1912). Emory and Salant, 1909, report experiments on the decomposition of caffeine in the liver. A trace appears in the stomach, intestines and in the bile. The gastro-intestinal excretion is higher when the kidneys are excised (Salant and Rieger, 1913). The loss of methyl groups occurs in pretty much all organs (J. Schmidt, 1910).

Methylated Uric Acid.—Hanzal, 1930, concluded that theophylline and theobromine are excreted, at least in part, as methylated uric acid. Methylated uric acids, when administered, are excreted for the most part unchanged. Those with CH_3 in the 7 position are not demethylated at all.

Uric Acid Level of the Blood.—Clark and Lorimeier, 1926, claim that this is increased by caffeine and by theobromine.

Passage across Placenta.—Fabre and Régnier, 1934, administering fairly large doses of caffeine to dogs, found the concentration in the fetal blood and liver as high as in the maternal.

Potentiation by Theophylline and Theobromine.—Froehlich and Zak, 1927, reported that theophylline increases the effects of a number of poisons, by facilitating their penetration into the central nervous system. Acid fuchsin, for instance, stains this more deeply and produces convulsions in smaller doses in frogs. Fluorescein stains more promptly and more intensely; ferrocyanide penetrates more rapidly. Morphine causes deeper narcosis in frogs, and magnesium in rabbits. Franceschetti and Nieland, 1928, reported that theophylline increases the excretion of arsenic into the cerebrospinal and intraocular fluids.

Theophylline on Absorption of Mercurial Diuretics.—The rapidity of absorption of mercurin and of salyrgan from intramuscular injections is materially increased by the addition of theophylline, due partly to the formation of complex nonprecipitant mercury compounds, partly to a buffer action A series of other organic substances have similar effects (De Graaf and Lehman, 1936; R. A. Lehman and Dater, 1938).

Toxicology.—The fatal dose of caffeine is so large (presumably about 10 Gm.) that fatal poisoning is rare; but doses above 1 Gm. may produce alarming symptoms, and even therapeutic doses may cause unpleasant *side actions*, especially in cardiac patients: palpitation, insomnia, nausea, vomiting, headache, vertigo, restlessness, anxiety and sometimes delirium. Theobromine is relatively free from these objections, but they may arise. They are also produced by theophylline (Widmer, 1914). The side actions occur much more violently, and with much smaller doses (0.3 Gm. of caffeine per day, or even less) in patients with *interstitial nephritis* (L. Taylor). (The doses are calculated on the basis of pure caffeine; the corresponding amounts of citrated caffeine would be twice as high.)

With *larger doses*, the pulse is full and hard, quickened or slowed, with palpitation and precordial distress (sometimes anginal attacks). The head is heavy, throbbing, confused; often intense headache and great anxiety. Restlessness and excitement, insomnia (sometimes mild delirium, aphasia, fever). Vertigo, nausea, general discomfort, fatigue, weakness (sometimes burning in the throat, gastric distress, heat flashes, perspiration, insensible pharynx, swollen tongue, ringing in the ears, flashes in eyes). Tremors of jaws, hands and feet, and muscular stiffness. Quickened, embarrassed respiration. Increased micturition (sometimes ardor urinae and erection). In *very severe cases* there is vomiting (sometimes violent diarrhea and tenesmus); violent choreic tremors. Collapse, with small, irregular arrhythmic pulse, cold extremities, dilated pupils. Consciousness is usually intact, but there may be delirium. Doses of 1 Gm. and higher have been taken to evade military service, especially by producing tachycardia (sometimes to 160 per minute). The drug is easily detected in the urine (Hollande and Thevenon, 1916).

The symptoms in animals are restlessness and increased reflexes; increased respiration, vomiting and diarrhea; muscular weakness. Then: clonic or tetanic convulsions, during which respiration may stop, with or without resumption; exhaustion and increasing paralysis; death in one to four hours. The fatal dose lies about 0.15 Gm. per kilogram. Dogs and cats are somewhat more susceptible than rabbits and guinea pigs. The dose by mouth is but little larger than the intravenous dose, except in rabbits (Salant and Rieger, 1910, 1912). Young mice are more resistant than old. The effects in *birds* are similar (Brill); in *frogs* they are modified by the onset of rigor. The toxicity for frogs is diminished by temperature above 98° F. At 45° F. the muscular effects predominate; while the convulsions become more prominent as the temperature is increased (Salant, 1913).

Recovery is usually complete within a day, even when the symptoms were violent. Some restlessness and weakness may remain for a time. It is claimed (Kunkel) that large therapeutic doses have been followed by nephritic urine, but on the other hand, daily doses of 1.25 Gm. have often been given without detriment (Becher, 1884). *Idiosyncrasy* toward caffeine is marked. Children and nervous and weakened individuals appear to be relatively more susceptible. Overdoses should be avoided, especially in *myocarditis*.

The *treatment* consists in evacuation and narcotics—bromide, alcohol, chloral or morphine. It is important to reassure the patient.

Theobromine and theophylline, in excessive doses or in susceptible individuals, may produce toxic effects similar to those of caffeine: headache, nausea, vomiting, epileptic spasms, albuminuria, gastric hemorrhage, etc. These manifestations are, however, rare. In epileptic patients, large doses of theophylline are said to have provoked attacks (Schlesinger, 1905). Two deaths from cardiac failure are attributed by Cadburg, 1918, to theophylline (about 1 Gm. in divided doses), but the patients were under digitalis treatment for heart disease and the causation is therefore rather doubtful.

The **differences in the members of the group** may be recapitulated: *Caffeine* has the most powerful central nervous action, with relatively weak peripheral effects. The strongest diuretic action is produced by *theophylline*, which also causes the most marked cardiac stimulation and coronary dilatation. Its central effects and its action on muscle approach those of caffeine. *Theobromine* acts most powerfully on muscle; its effects on the heart and urine are intermediate. It causes little central stimulation.

The pharmacology of theobromine was first investigated by Mitcherlich, 1859, and further by Filehne, 1886. It was used experimentally as a diuretic by von Schroeder, 1887, to avoid the supposed vasoconstriction of caffeine.

This led to its clinical introduction by Gram. The toxicity of theobromine to isolated muscle is one hundred and twelve times that of caffeine (Velly and Waller, 1910).

PREPARATIONS.—***Caffeine**, U.S.P. (theine, trimethylxanthine), is a feebly basic alkaloid, usually prepared from tea. It is a white, odorless powder and has a slightly bitter taste. It is fairly sol. in water (1:50) and in alc. Its solubility in water is greatly increased by heat, citric acid, benzoates or salicylates, bromides, antipyrine and a number of other substances. Incompatible with tannin. Dose, 0.12 to 0.3 Gm., 2 to 5 grains, in capsules. *Citrated Caffeine*, U.S.P., is generally used for oral administration in solution. It is a mixture of caffeine and citric acid, containing about 50 per cent of caffeine. It gives a clear, syrupy solution with a little water, but precipitates on dilution. The precipitate redissolves on the further addition of water, the solubility being about 1:32. Incompatible with carbonates. The dose is somewhat less than twice that of caffeine. The free acid renders this unsuitable for hypodermic use. *Caffeine and Sodium Benzoate*, U.S.P., is the most suitable compound for hypodermic injection. It is a mixture of equal parts of caffeine and sodium benzoate. Freely sol. in water (1:1.1) with practically neutral reaction. Dose, orally or by injection, 0.15 to 0.5 Gm., 2½ to 7½ grains. *Caffeine and Sodium Benzoate Injection*, U.S.P., is usually available as 0.25 or 0.5 Gm. in 2 cc. of water for injection.

Theobromine, a dimethylxanthine prepared from cacao seeds or synthetically, is only slightly sol. in water. It is usually administered as ***Theobromine and Sodium Acetate**, a hydrated mixture of theobromine sodium and sodium acetate, containing 60 per cent of theobromine. Freely soluble in water (1:1.5) with alkaline reaction. *Dose*, 0.5 to 1.2 Gm., 8 to 20 grains, well diluted. It gradually absorbs carbon dioxide from the air with the liberation of theobromine, becoming partially insoluble in water. It must therefore be protected against exposure to air, and is *incompatible* with acids and with chloral. It should not be given with meals, to avoid precipitation by the gastric juice. Solutions do not keep. *Theobromine and Sodium Acetate Capsules*, U.S.P.; usual sizes, 0.1 and 0.2 Gm. *Theobromine with Sodium Salicylate*, N.F. (*diuretin*), is a mixture of sodium theobromine and sodium salicylate in nearly equal molecular proportions. Dose, 1 Gm., 15 grains.

Theophylline, U.S.P. (theocin), is also a dimethylxanthine. It is sparingly sol. in water (1:120) and alc.; freely sol. in alkalis. Dose, 0.25 Gm., 4 grains, three times a day in warm tea. After two or three days it should be replaced by theobromine. *Theophylline Tablets*, U.S.P., are usually available as 0.1 and 0.2 Gm. It may be given in solution as ***Theophylline and Sodium Acetate**, U.S.P., containing about 60 per cent of anhydrous theophylline. Sol. in water (1:25) with alkaline reaction; insol. in alc. Bitter, salty taste. Dose, 0.12 to 0.3 Gm., 2 to 5 grains. *Theophylline and Sodium Acetate Tablets*, U.S.P., are usually available as 0.1 and 0.2 Gm. ***Aminophylline** (theophylline with about 13 per cent of ethylene diamine) contains about 75 per cent of anhydrous theophylline with ethylenediamine, $C_2H_4(NH_2)_2$. White or yellowish granules, slight ammoniacal odor, bitter taste. Sol. in water (1:5) with alkaline reaction; insol. in alc. Dose, 0.1 to 0.2 Gm., 1½ to 3 grains, three times daily by mouth (preferred); 0.5 Gm. per day intramuscularly; 0.25 Gm. by vein. *Aminophylline Tablets*, U.S.P., are usually available as 0.1 and 0.2 Gm. *Aminophylline Injection*, U.S.P., is usually available as ampuls, 0.25 Gm. in 10 cc.; 0.5 Gm. in 2 cc. and in 20 cc. There are generally no ill effects, even after long-continued use. It may be injected into the gluteal muscles, 1 to 3 ampuls of 0.5 Gm. in 2 cc., per day. Intravenous injection should be used only in acute emergenices, 0.25 Gm. in 10 cc. It may be administered by rectum, 2 to 4 suppositories of 0.36 Gm.

Boerhaavia diffusa, an East Indian weed (Punarnava), contains a diuretic alkaloid. It produces some rise of blood pressure, but this is not the main mechanism of the diuresis. Clinically, the fluidextract is an effective diuretic in ascites and edema, especially in early liver, peritoneal or renal disease, and more effective than other diuretics in early hepatic cirrhosis and chronic ascites; but it has relatively little effect in cardiac disease (Chopra *et al.*, 1923).

Albamyricetin, a glucoside from the blossoms of a tropical tree, is strongly diuretic, depresses excised intestine and blood vessels, and inhibits the heart (Abe and Takahira).

Caffeine Beverages.—The annual per capita consumption in the United States is about 10 pounds of coffee and 1 pound of tea (Graham, 1912). A cup of coffee, prepared from 15 to 17 Gm., or strong tea contains about 0.1 Gm. (1½ grains) of caffeine; average tea, 60 to 75 mg. (Punnet, 1942). Its effects are somewhat modified by the associated products (the volatile products causing more psychic stimulation, the tea tannin and coffee oil deranging digestion), but essentially the actions are those of the alkaloids. They consist in increased mental and physical efficiency by psychical stimulation, comfort, and relief from muscular and mental fatigue and from their attendant unpleasant sensations. These effects may be useful in certain conditions, as in those exposed to severe hardship, hunger, fatigue; but caffeine lowers performance in work requiring fine coordination, as in marksmanship (Graf and Muller, 1938). Ordinarily these beverages are pleasant luxuries which may do no harm if the consumption is kept within bounds; but nervous individuals, who are the most liable to be injured by caffeine, are most likely to exceed these bounds. The bad effects are usually not very serious, and disappear promptly if the habit is discontinued. They consist in nervousness, tremor, palpitation, insomnia, headache and digestive disturbances. The habitual consumption of caffeine confers a limited tolerance. Its withdrawal does not produce any marked abstinence symptoms. Coffee and chocolate are *useful flavors* and extemporaneous vehicles, especially for castor oil and cod liver oil.

Coffee (Caffea) consists of the dried seed of Caffea Arabica, Rubiaceae. The constituents of the "green bean" are caffeine, fat, coffalic and chlorogenic acid, saccharose, etc. The *chlorogenic acid* gives a green color with iron, similar to tannic acid, and in its impure form it was formerly called "*caffeotannic acid.*" Gorter, 1910, found it in about 100 plants. On oxidation it yields caffeic acid. It differs from tannins in that it does not precipitate proteins, and is therefore not astringent. The *percentage of caffeine* varies in different specimens from $\frac{2}{3}$ to $2\frac{1}{2}$ per cent, usually about 1.2 per cent (Koenig). It exists mainly as caffeine-potassium chlorogenate (Gorter, 1908). In the process of *roasting* (*i. e.*, heating the seed to 200° to 250° C.) a small amount of caffeine is volatilized; but since about 10 per cent of water is driven off, the percentage of caffeine is actually a trifle higher (1.25 per cent). The main change in roasting consists in the production of aromatic, brown and oily products. This oil (*caffeol* or *caffeon*) consists of 50 per cent of furfurol alcohol, and small quantities of valerianic acid, phenol, pyridine and a nitrogenous aromatic substance (Grafe, 1912). It is probably derived mainly from the hemicellulose. *The beverage, coffee,* is a decoction made with 6 to 10 per cent of the drug. Practically the entire caffeine (perhaps $\frac{9}{10}$) is thus extracted. The use of coffee arose in Arabia and Egypt about the middle of the fifteenth century. Coffee and tea were introduced into Europe about the last quarter of the seventeenth century, about the same time as the potato, cinchona, tobacco and chocolate.

Action of Coffee Oil.—The volatile aromatic constituents produce local irritation and reflex stimulation, in the same manner as condiments. The hot water contributes to this effect; and possibly the greater reactivity induced by the caffeine heightens the reflex response (Schmiedeberg). The local irritation stimulates peristalsis, and excessive use tends to nervous dyspepsia. It is doubtful whether the quantities taken in the beverage cause any direct central stimulation.

Wilhelm, Rorer and Reichert did not obtain any effects with coffee distillates. I. Lehmann, Archangelsky, Hare and Marshall, and Erdmann found, with *small doses:* pleasant stimulation; increased respiration; increased heart rate, but fall of blood pressure; muscular restlessness; insomnia; perspiration; congestion. *Large doses:* increased peristalsis and defecation; depression of respiration and heart; fall of blood pressure and temperature; paralytic phenomena. Grafe, 1915, believes that the products of roasting contribute to the action.

Decaffeinated Coffee.—In the commercial brands the caffeine has been reduced to insignificant proportions; for instance, by extracting the steamed green coffee with trichloroethylene, as in Kaffee-Hag. Such coffees produce practically no effect on the blood pressure, pulse rate, response to motor tests, or oxygen consumption (Horst *et al.*, 1934 and 1936; Haldi *et al.*, 1944). They accelerate propulsion in hypotonic stomachs less than does ordinary coffee (A. W. Bauer, 1928), but in hyperchlorhydria and gastric ulcer, they stimulate gastric secretion about like ordinary coffee (Bernay and Faure, 1937).

H. Gummel and Kiese, 1938, conclude that the motor excitement (in rats) is due solely to the caffeine, and that the effects of intravenous injection of coffee decoction on blood pressure and on isolated organs are due solely to choline and related substances, which had been isolated chemically by Li, 1937. Aubert had attributed the intravenous toxicity to potassium.

Tea (Thea) consists of the dried leaves of Thea sinensis, Theaceae. It contains caffeine (1.4 to 3.5 per cent, usually 2 to 3 per cent); tannin (1 to 30 per cent); traces of theobromine, theophylline, xanthine, adenine and volatile oil. The black and green teas differ only in the treatment to which the leaves are subjected—a fermentation with the black variety, which mainly alters the color and flavor; the green tea is rather more rich in volatile oil. The beverage is a 1 to 4 per cent infusion. A cup of strong tea prepared from 5 Gm. of leaves contains about 0.1 Gm. of caffeine (Aubert). A quick infusion extracts practically all the caffeine, but only a part of the *tannin* (which is especially abundant in the finer sorts). The customary brief infusion is therefore commendable, since the tannin may be deleterious to digestion, by precipitating proteins and albumoses, by lessening absorption and by irritating the gastric mucosa. The *tea distillate* is credited by Archangelsky with actions similar to those of caffeol. Lehmann and Tendlau found it inactive.

Cola (Kola, the seed in Cola acuminata, Sterculiaceae) is used by the natives of Africa, the fresh and often germinated seed being chewed. The dried seed, which has been introduced as a popular "tonic," contains caffeine ($1\frac{1}{2}$ to $3\frac{1}{2}$ per cent, usually $2\frac{1}{3}$ per cent); theobromine $\frac{1}{40}$ per cent); tannin (Kola red); fat, sugar, etc. In the fresh nut, the caffeine is combined with a glucosidal tannin ("kolatin," Goris, 1907). This compound, which was formerly termed "kolanin," is partly decomposed in drying, by an oxidase, into free caffeine, glucose and Kola red (Chevrotier and Vigne, 1907).

Guarana, a dried paste, prepared by the Indians of South America, consists chiefly of the dried and pounded seed of Paulinia cupana, Sapindaceae. It contains 4 to 5 per cent of caffeine, tannin, etc. Dose, 2 Gm., 30 grains. **Maté** (Paraguay tea) consists of the leaves of Ilex paraguayensis. It contains 0.13 to 1.85 per cent caffeine (2 per cent, Bertrand and Devuyst, 1910), 10 to 16 per cent of tannic acid, etc. It is used in South America for preparing a beverage.

Cacao is consumed extensively as a beverage and in the form of chocolate, a mixture of melted cacao and sugar, often with the addition of flavors, starch, etc. It contains theobromine, instead of caffeine, and therefore acts less on the nervous system. It is also rich in fat, which is nutrient. A part (about half) of this fat (Oleum Theobromatis or Cacao Butter) has been removed from the commercial powdered cacao. The name Cacao should not be confused with Cocoa (the palm yielding the cocoa nut), nor with Coca, the source of cocaine. Cacao consists of the fermented, dried and often roasted seed of

Theobroma Cacao, Sterculiaceae. It contains theobromine ($1\frac{1}{2}$ to $4\frac{1}{2}$ per cent, usually $1\frac{1}{2}$ per cent); a trace of caffeine; 50 per cent of fat; starch, tannin, etc. The theobromine is liberated from a glucoside during the fermentation. The fat is generally considered rather indigestible, but Neumann, 1906, showed that it is digested as well as other fats.

Chicory. The roasted root of this plant is used as substitute for coffee. It probably contains similar empyreumatic substances, but no caffeine. Schmiedeberg, 1912, considered it a harmless stimulant, stomachic and antiseptic. C. Reynolds, 1930, believes that it has no pharmacological significance. Still less is known about roasted malt and other cereals which are used as *coffee substitutes.*

Phenomena of chronic caffeine poisoning have been described most commonly in excessive tea drinkers (Bullard, 1886). The first symptoms are usually dyspeptic—epigastric uneasiness after meals, and a general lowering of the mental and physical tone. This is succeeded by restlessness and nervous excitability, tremors and disturbed sleep, soon followed by anorexia and by headache, vertigo, confusion. Constipation is common, but not more so than in individuals not addicted to tea. Palpitation, generally associated with irregularity, becomes distressing, and is often accompanied by dyspena. In severer cases these symptoms are aggravated and continuous. Neuralgic, sensory and hysterical disturbances are common, but it is not easy to say whether these are the cause or effects of the caffeine habit.

The quantity of tea required to develop these symptoms varies with the individual. The daily average consumption of Bullard's patients was five cups, which corresponds to about 0.6 Gm. or 8 grains of caffeine. The susceptibility is much greater in youth, anemia, weakness, insufficient food, exhaustion, and in "nervous" individuals. Children who drank coffee were reported by Taylor, 1912, to average below the normal weight, height and strength.

Differences between Tea, Coffee and Cacao.—The effects of excessive coffee consumption differ only in details from tea. Both interfere with digestion, the coffee through the irritant effects of its volatile oil, the tea through the coagulant action of the tannic acid. The caffeine itself probably contributes to the digestive derangement through its vasodilator action. This may account for the common tendency to hemorrhoids. Cacao may disturb the digestion through its richness in fat, but other symptoms are not common, partly because there is less inclination to its excessive use.

The Acute Effects on Digestion.—Caffeine causes a considerable flow of gastric juice in man, not in dogs. This effect is also produced by caffeine-freed coffee and by beverages prepared from roasted cereals. In terms of free acid the order is: Coffee, 100; Coca Cola, 90; Sanka, 75; tea, 60; coffee with cream, 60; Postum, 60 (J. A. Roth *et al.,* 1944). A liter of coffee or tea, hot or cold, taken with meals, has no definite effect on the acidity or the evacuation time of the stomach. Cacao, $\frac{1}{2}$ to 1 liter, decreases the acidity and delays evacuation (R. J. Miller *et al.,* 1920), presumably through its fat.

Chronic Caffeine Poisoning in Animals.—Salant and Rieger, 1910, found that continued administration of doses which did not cause acute effects, eventually produced emaciation, often ending in death. The stomach and, to a less degree, the intestine showed inflammatory changes. Habituation increased the tolerance to acute poisoning, the fatal dose being 15 to 80 per cent larger than ordinary. Gourewitsch, 1907, also claims a "histogenetic" habituation. Mice kept continuously under caffeine were found to exhibit less than the normal activity, but showed a normal gain in weight (Nice, 1912). Large doses of caffeine beverages decreased the growth rate of young rats, and somewhat decreased the average number of fetuses (Hamill and Miller, 1935).

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ADENYL COMPOUNDS

These include adenine, adenosine and other purine derivatives of nucleic acid which are contained in tea and obtained from other sources, and some synthetically. In general, they dilate the coronary vessels, depress and slow the heart, lower blood pressure, inhibit intestinal and stimulate the ureteral movements, and produce leukocytosis (reviews, Drury, 1936; R. Rigler, 1938). The relation of the adenylic system to phosphorylation is discussed under phorphorus compounds.

Adenine, a purine base, has a low toxicity, but large doses produce enteritis, and uric acid infarcts of the kidneys.

Adenylic Acid is a phosphate ester ("nucleotide") of adenine with the pentose d-ribose. It acts on the myocardium and on arterial and other smooth muscle, varying with the organ (review, R. Rigler, 1938).

Coronary Dilatation.—A. M. Wedd, 1931, reported that *adenosine* produces marked increase of coronary flow (twenty times that of nitrite) in perfused rabbit heart, independent of changes of rate or excursions, and antagonistic to the constrictor action of pitressin or barium. Similar but somewhat less potent dilatation was produced by adenylic acid, adenine and guanosine. Wedd and Drury, 1934, confirmed the increase of coronary flow by intravenous injection in dogs, notwithstanding the fall of blood pressure; but intramuscular injection was ineffective. The coronary dilatation improves the *functionation of the heart,* in intact animals or perfused, especially when it has been depressed, as by mecholyl or exhaustion (Wedd, 1935). Adenylic acid appeared beneficial in a case of clinical paroxysmal tachycardia. Adenosine produces bradycardia and A-V block in man and in rats (Kalaja, 1938). The direct action on the heart (by immersion of turtle or mammalian heart) is purely depressant (Wedd and Fenn, 1933). *Adenosine triphosphoric acid* is more active than any of its compounds in producing intererence with cardiac conduction, and increasing tone of excised guinea pig uterus (Deuticke, 1932). Its potency is diminished by deaminization. Removal of PO_4 from adenosine increases its ability to lower blood pressure and to dilate the coronary vessels. This is greatly diminished by deaminization (Gillespie, 1934). The depressor substance of blood was identified as adenosine triphosphate by C. H. Fiske, 1934. Intravenous injection of adenosine triphosphate produces the clinical features of circulatory shock; and as it is released from muscles by injury, it may play a part in shock by muscle trauma (Bielschowsky and Green, 1943).

Adenine, allantoin and hypoxanthine increase the inhibitory response of the turtle heart to *acetylcholine and vagus stimulation* (A. Lamalle, 1941).

Protection against Liver Necrosis.—*Sodium xanthine*, administered hypodermically to rats before exposure to chloroform or carbon tetrachloride, decreases the necrosis of the liver lobules and lowers the mortality rate. It does not stimulate the regeneration of the cells (Neale, 1937; O. G. Fitzhugh, 1938; J. C. Forbes, 1939). Other purine derivatives are also protective (nucleic acid, guanosine, guanine, hypoxanthine; uric acid slightly), but allantoin and alloxan increase the liver damage (R. C. Neale and Winter, 1938). Ravdin *et al.*, 1939, attribute the protection to protein cleavage products resulting from the local inflammatory action, since the effect is also produced by other irritants.

Allantoin has the same effect as living maggots on suppurating wounds and resistant ulcers, removing the infected material and stimulating growth of healthy connective tissue, and so promoting healing. The action lasts only while it is in actual contact with the granulating tissue. It is applied by soaking the bandages in 0.4 per cent solution, freshly made in hot (but not boiling) water (W. Robinson, 1935; Kaplast, 1937). However, in 1936 Robinson concluded that it does not act as such but by conversion into urea, and proposed to use this instead of allantoin, as equally effective and much more economical. Clinical reports from allantoin are scanty (review, Council on Pharmacy and Chemistry, 1938, J.A.M.A., *110*: 813). Shipp and Hetherington, 1936, obtained practically no stimulation of growth of fibroblasts with chicken heart cultures on addition of ½ per cent of allantoin.

Allantoin, glyoxyldiureid, is widely distributed in animals and plants. It is the end product of purine metabolism, by oxidation of uric acid through uricase, in animals below apes and man. It occurs as a white powder, slightly soluble in water, and is not toxic.

Alloxan produces experimental diabetes by necrosis of the islets of Langerhans (see Index).

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OPIUM, MORPHINE AND RELATED ALKALOIDS

Morphine and the related alkaloids of opium (the coagulated juice of the incised seed capsules of the opium poppy) have peculiar effects on the psychic functions, which render these more tolerant to discomfort and pain. This gives them a wide field of usefulness, especially in symptomatic therapeutics; but it also leads easily to their abuse, too often with tragic results. Larger doses are toxic mainly by depressing the respiration. The spinal cord is stimulated. Therapeutic doses also suppress intestinal peristalsis chiefly by peripheral action.

Origin.—The opium poppy is cultivated in Asia and Egypt; it can be raised in the United States, but the cost of labor renders the production of opium unprofitable: Thoms found that it requires 283 hours of labor to collect a kilogram of opium! The dried plant capsules (especially before ripening, Caesar and Loretz, 1902) and seed also contain the alkaloid; the poppy straw is a commercial source of morphine, but of minor importance, as it contains only 0.3 per cent of total aklaloids, while official opium contains about 10 per cent of morphine. The alkaloids are not present in the fresh plant, but are produced by the action of oxidases on the latex (True and Stockberger, 1916). The seeds yield 50 per cent of a bland fixed oil which may be used like olive oil.

Historical.—The word "mekonion" was applied in ancient Greece to three substances, (1) poppy juice; (2) Euphorbia peplus, a drastic purgative; (3) the excrement of newborn children. About 380 B.C. Diagoras of Melos describes the collection of opium by incising poppy capsules. Opium is also mentioned by Theophrastus, third century B.C. A further account of its history is given by Macht, 1915. The history of the opium preparations is interesting (Wilbert, 1916). "*Laudanum*" is said to have been originated by Paracelsus (1493–1541), but as a solid aqueous extract; "*paregoric*" by Le Mort of Leyden, early in the eighteenth century. "Sydenham's laudanum" (Vinum Opii) is derived from a formula of Sydenham (1624-1689). Tr. Opii Deodorati was originated by Robiquet (1780-1840), and Robert Hare, 1827; "Brown Mixture" by Dr. B. J. Barton of Philadelphia, about 1814.

Opium Alkaloids.—Opium contains two chemically distinct groups of alkaloids. The group of morphine, or the *phenanthrene derivatives*, is by far the more important. It comprises morphine and the esters formed by replacing the H of one or both hydroxyls of morphine. Some of these occur naturally in opium (methyl-morphine or codeine, dimethyl-morphine or thebaine). Others are produced synthetically (ethyl-morphine or dionin, diacetyl-morphine or heroin, etc.).

The second group, or *isoquinoline derivatives*, is represented by papaverine and narcotine. They are not narcotic, but act chiefly as rather feeble relaxants of smooth muscle. Similar alkaloids preponderate in other plants of the poppy family.

Chemical Structure of Morphine Alkaloids.—This is definitely established, but it has not yet been successfully synthesized. Morphine has two hydroxyls, one phenolic, the other alcoholic. Either or both of these may be replaced by other radicals, as in the derived alkaloids that occur in opium, and other changes may be made artificially. Numerous derivatives have been prepared, especially by Small and Mosettig, and investigated pharmacologically by Eddy and his collaborators for the Narcotic Addiction Committee of the National Research Council with the hope that it might be possible to obtain materially more favorable relations of the therapeutic to the addictive actions than exist in the natural alkaloids.

Absorption, Fate and Excretion.—Morphine is rapidly absorbed from all mucous surfaces and from the abraded skin, but scarcely, if at all, from the intact skin. It passes from the blood into the tissues, where it is temporarily stored. Half to two-thirds is excreted by the urine, part free and part conjugated; a much smaller amount by the feces and other secretions. The remainder is destroyed in the tissues, chiefly in the liver. Habituation and acquired tolerance do not alter the fate materially. Theories that attribute acquired tolerance to increased destruction of morphine are not tenable, in view of the fact that the tolerance is practically as great with intravenous injection, *i. e.*, before any morphine could be destroyed; and that some of the functions, for instance that of the vagus center, do not participate in the tolerance, as they would need to do if the destruction of the morphine were increased.

Isolation, Tests and Estimation of Morphine in Biological Fluids.—The results of earlier investigations on the fate of morphine have been largely discredited. Concordant results have been obtained by the modern methods as described by G. A. Emerson, 1934; J. W. Mull, 1938 (10γ in 4 cc. of blood); W. Deckert, 1936 (effective for 10γ in 1 to 10 cc. of urine); F. W. Oberst, 1943 (0.03 to 0.2 mg. in organs). It is now possible to diagnose addiction clinically by testing the urine (S. To, 1935), and even to approximate the quantity of morphine which is being taken (S. To and Ri, 1937).

Excretion.—The most satisfactory studies have been made on thoroughly habituated men and dogs, which tolerate relatively large doses, without functional disturbance. It has been contended that habituation involves alterations in the excretion of morphine, but this was based on imperfect chemical methods; there were no good studies on nonhabituated human individuals, and none on animals, with doses that did not involve toxic effects: diarrhea, coma, depressed metabolism, etc., which introduce complications that are probably much more profound than habituation.

Conjugation.—Urine hydrolyzed with dilute acid yields two to twenty times more morphine than before hydrolysis. The ratio of conjugated morphine decreases with induced tolerance (V. Thompson and Gross, 1940; Oberst, 1940). Both OH groups of morphine are involved in the conjugation. The conjugation is decreased by damage to the liver, both in habituated and nonhabituated, so that the excretion of free morphine is increased at the expense of the conjugated, the total excretion remaining unchanged (E. G. Gross, 1942). Diacetyl morphine and codeine, as well as morphine, are excreted chiefly in conjugation; dihydrocodeine and its methyl ether are chiefly free (Oberst, 1941).

Morphine Excretion by Habituated Man.—The urinary excretion of total morphine averages about 65 per cent with the dosage of 20 mg.; 43 per cent with 65 mg. (A. J. Eisenman, 1945). The unconjugated morphine averages 2.7 per cent of the oral dosage; codeine, 4.3 per cent; with hypodermic administration, the average is 5.4 per cent for morphine, 5.9 per cent for codeine. The excretion decreases promptly on withdrawal and stops in five days. Only traces appear in the feces (Himmelsbach *et al.*, 1940).

Morphine Excretion in Dogs.—E. G. Gross and Thompson, 1940, recovered 80 to 90 per cent of the injected morphine, mostly conjugated, regardless of dosage. With dogs that had acquired tolerance by habituation for one or more years, the total excretion was reduced to 35 to 65 per cent, the decrease being chiefly in the combined form.

Excretion into the Digestive Tract.—Morphine is excreted by the mucous membrane of the entire gastrointestinal tract, and may appear in the large intestine before it can be demonstrated in the small intestine, after intravenous injection (Marquis, 1896). The bile contains only traces (Kauzmann, 1868; Hatcher and Gold, 1929). It is also excreted by the saliva (Rosenthal, 1893), and by the stomach (Marmé, 1883); but only traces can be found in the stomach after hypodermic administration of toxic doses, in man as well as in animals (Hatcher, 1924; Hatcher and Davis, 1926; P. Ellinger and Seeger, 1934), so that it would be useless to treat hypodermic morphine poisoning by gastric lavage, as had been advocated by Alt, 1889, and practiced for many years (Langer, 1912; Kleiner, 1913).

Excretion by Milk.—It has been claimed that this causes morphinism in the nursling; but Koldewyn, 1910, after the administration of morphine to cows and goats, could not demonstrate it in their milk. The quantity is probably insignificant. There is no question that morphine passes through the placental circulation into the fetus, sometimes causing death in the uterus (Jung, 1913), and distinct tolerance in the newborn of animals habituated to morphine (K. Rei, 1937).

Distribution in the Tissues.—Morphine leaves the blood rapidly, although it is not destroyed by it (Cloetta, 1903). The distribution in human morphine addiction is reported by F. W. Oberst, 1943. With intravenous injection, only traces remain after two to ten minutes in cats, after thirty minutes in dogs (Hatcher and Gold, 1929), the blood being then presumably in equilibrium with the tissues. When added to shed blood, it is equally divided between corpuscles and plasma (Teruuchi and Kai, 1927). In general, the largest quantity is in the skeletal muscles; then the kidneys, liver and intestinal contents, the brain contains very little, less than the blood, even in severe poisoning (Hatcher and Gold, 1929; P. Fleischmann, 1931). The recovery after burial has been investigated by

Homburger and Munch, 1916, and by Palet, 1919. The latter obtained positive tests after seven months.

Destruction in the body proceeds rather slowly; a third or more of a large dose may be recovered from the animals, habituated as well as nonhabituated, killed twenty-four hours after the injection (Cloetta, 1903; Rübsamen, 1908). With ordinary doses the storage is not large, for the withdrawal symptoms of addicted persons appear in about twelve hours, and the amount in the urine drops promptly. Habituation does not appear to alter the destruction of morphine materially, nor does hyperthyroidism; but dinitrophenol caused a marked decrease of morphine excretion in normal dogs (O. H. Plant and Slaughter, 1937). The liver plays an important part in the destruction: liver damage increased the excretion by an average of 43 per cent in habituated and nonhabituated animals (E. G. Gross, Plant and Thompson, 1938). Defibrinated blood does not destroy morphine (Cloetta, 1903; Teruuchi and Kai, 1929); on perfusion through the liver, morphine is rapidly fixed and destroyed, the rate being the same in habituated as in nonhabituated animals (Hatcher and Gold, 1929). Cloetta, 1903, reported considerable destruction of morphine by digestion with oxygenated emulsions of lung, liver and especially brain; filtered extracts did not have this effect. Morphine and dilaudid are also oxidized by slices of rat liver, apparently at the hydroxyl group. This does not occur anaerobically or on boiling, nor by kidney or brain tissue. It is inhibited by monoiodoacetate, fluoride and cyanide (F. Bernheim and Bernheim, 1945).

Fate in Chick Embryos.—If morphine is injected into fertilized eggs, which are then incubated, no destruction of morphine or its derivatives occurs if the embryo dies before it is half developed. If the development is completed, heroin is destroyed absolutely; morphine very largely, codeine and dionine not at all. The alkyl groups protect the morphine against oxidation, as they do in the adult organism, while the acetyl groups are easily separated (Grueter, 1916).

Fate in Frogs.—In these, the destruction is small and no tolerance is acquired. The excretion is slow, extending over eight days, and occurs exclusively through the alimentary tract (B. Frenkel, 1910).

Fate of Codeine.—Codeine is excreted as such in the urine without demethylation. The percentage excreted by addicted persons is but slightly greater than for morphine (Himmelsbach *et al.*, 1940), but dogs are reported to excrete about 80 per cent, mainly in the urine, somewhat also in the feces (Tauber, 1892). Repeated administration does not increase its destruction, nor does it appear to produce tolerance in animals (Bouma, 1903).

Fate of Heroin.—The greater part is excreted unchanged in the urine; some also in the feces. A part is destroyed, and this destruction was said to be increased in habituation (Langer, 1912). Human and other mammalian tissues contain enzymes capable of splitting off the acetyl group. Their content is highest in the liver, then the kidneys (C. I. Wright, 1942).

Odorous Substances.—The substances which give the characteristic odor to opium are excreted largely by the urine and also in the breath, sweat and milk.

Central Nervous System.—The most important actions of morphine are on the central nervous system. It depresses the brain, especially its higher functions. The medullary centers are first stimulated, then depressed. The reflexes and the spinal functions are mainly stimulated. The effects are broadly identical in all vertebrate animals, although the dosage varies greatly, and the symptoms show considerable differences in the relative prominence of certain phenomena and in the time required to produce the successive actions. The descending depressant action of morphine is illustrated by the frog, in which the development of the symptoms corresponds closely to those produced by progressive removal of the brain. This is also the general course in mammals, though the symptoms are more confused. The difference is explained by the more rapid action of the drug, and by the more intimate correlation of the nervous centers.

Effects of Morphine on Frogs.—After doses of 20 to 50 mg. the symptoms start with diminution, and then absence, of voluntary movements, but the animals react normally when stimulated. (This corresponds to ablation of the hemispheres.) The frog sits quietly in the normal position; he will climb up an inclined plane and give the croaking reflex when stroked. When placed in a tumbler filled with water and inverted in a large vessel of water, it will leave the glass to seek the air. As the narcosis deepens, it will remain under the glass. Placed on the table, its leaps become more and more clumsy, and it does not avoid obstacles in jumping (corresponding to excision of the corpora quadrigemina). Then the animal fails to leap even when stimulated (paralysis of cerebellum); but when turned on its back, it will resume its normal sitting position. This reaction also becomes more and more delayed and can be obtained only by reinforcing the stimulation through pinching, etc., until finally it fails altogether (paralysis of medulla oblongata). The reflexes are weakened, but present. The respiration is decreased.

Morphine Tetanus in Frogs.—After the frog has remained in this depressed condition for some time (a few minutes to several hours; the shorter, the larger the dose), the respiration becomes spasmodic, resembling superficially the Cheyne-Stokes type; then the spinal reflexes return; and the frog passes gradually into a tetanus of the strychnine type, located in the spinal cord. The delayed appearance of this tetanus is due to the slow absorption of the effective dose, for it appears at once on intravenous injection (Stockman and Dott, 1890). The convulsions occur more promptly if the heart is tied off (Githens and Meltzer, 1911), presumably because thus a larger proportion of the morphine reaches the nervous axis (Abel, 1912). The onset is hastened and the necessary dose reduced, by cold and by removal of the cerebrum, which inhibits convulsions. The results are prompter if the medulla is not destroyed (Githens, 1913). McGuigan and Ross, 1915, found that the previous injection of morphine sensitizes frogs to *strychnine* so that strychnine tetanus develops more quickly—provided that a latent period of one-half to two hours elapses between the morphine and strychnine injections. Morphine also increases the toxicity of *picrotoxin* for white mice (Pulewka, 1927).

Death.—The tetanus is mixed with paralytic phenomena, the animal lying lax between the spasms. Eventually the paralysis becomes permanent and ends in death. The *heart* is still beating at this stage and is indeed little affected directly. The convulsive stage may be absent with very large or very small doses.

Recovery.—If recovery occurs, the depressed functions recover in inverse order to their appearance (Witkowski, 1877; this paper also gives the older bibliography of the experimental work with morphine.)

Invertebrates do not show typical morphine effects.

Narcotic Symptoms in Human Subjects.—The first effect, produced by doses too small to elicit any other symptoms (5 mg.), consists in diminished sensibility to lasting impressions, expecially such as give rise to pain, cough, fatigue, hunger, discomfort and other disagreeable sensations. This tends to produce a state of emotional tranquillity, equanimity, well-being and buoyance (euphoria), sometimes of elation and ecstasy, especially with larger doses. These vary in degree and in kind with the individual disposition and with circumstances. On repeated use, the brain learns quickly to discount the inattention, thus establishing tolerance to increasing doses. Somewhat larger doses (10 mg. or more) depress the attention and thus weaken the appreciation of other external impressions. A sudden stimulus evokes a normal or exaggerated reflex response; there is even increased acuteness of perception of external impressions (Kraepelin, 1892); but persistent or gradual stimuli are neglected. The stimuli are evidently transmitted to the brain, but do not fix the attention through the mental fog. The faculties of concentration, of judgment and of memorizing (Weygandt, 1903) are all seriously disturbed, constituting a narcosis (torpor). Through this exclusion of external stimuli, the patient is quieted, and then passes through a dreamy, apathetic, drowsy, lethargic state into natural sleep. Exceptionally, the disturbed balance of the brain leads to excitement (especially in cats) and even to delirium. *Large doses* cause a much more extensive depression, the sleep becoming so profound that the patient can be aroused only imperfectly and wiht difficulty. Eventually the coma and insensibility are complete. *The special senses* are not affected directly. They may appear disturbed through the impaired attention, or through the heightened reflex irritability.

Excitant Effects in Man.—Some individuals, particularly among women, are more excited than depressed by morphine. This can perhaps be explained by diminished restraint, rather than by direct stimulation. The same explanation probably holds true for the flights of imagination which fill the period preceding the sleep. Occasionally morphine produces violent sensations of pain, heat, and itching (C. Jacoby, 1934). It has been stated that Malays are especially liable to morphine excitement, but hospital experience in Manila demonstrates that their reaction (to 0.01 Gm. hypodermically) is not different from that of other races (Dr. Jesus Celis, personal correspondence).

Electroencephalograms show decreased height and frequency of the alpha waves, and with deep sleep these aggregate into groups (H. Berger, 1934). In addicted individuals a stabilizing dose of morphine or codeine increases the ratio of occipital alpha waves and diminishes their potency (H. L. Andrews, 1940).

Psychologic Experiments.—Macht and Isaacs, 1916 and 1917, claim that in man 4 to 8 mg. at first shorten the reaction time. This is often followed after one-half hour by delayed reaction. With larger doses the primary stimulation is short and may be absent; and the secondary depression is predominant. Association (arithmetic) is delayed more readily and mistakes are more numerous than are simpler reactions. The lethargy is illustrated by the observations of Eddy and Simon, 1932, on rats trained to run a maze: morphine lengthened chiefly the "initial delay," *i.e.*, the interval before the rat decides to start on its path for the food. The "active time" was but little increased and errors not at all. With cats, morphine, 1 mg. per Kg., causes disappearance of learned adaptive response in the order of complexity and recentness of acquisition. Neurotic behavior is generally diminished (Wikler and Masserman, 1943). The *aphrodisiac effects*, which occur in some, and the anaphrodisiac action in others, depend upon the action on the imagination. With chimpanzees, erection occurs regularly a few minutes after injection of morphine and persists for an hour or longer. Addicted males are conspicuously averse to intercourse during the withdrawal discomfort (Spragg, 1940).

The reactions of young tame *chimpanzees* to hypodermic injection of morphine are described by Spragg, 1940. With 0.1 to 0.9 mg. per Kg. sedation is not observable, nor any constant or marked change in the pupils, nor in the gastro-intestinal tract, saliva or appetite. A wheal appears at the site of injection and there is marked generalized scratching, beginning in ten to fifteen minutes and lasting an hour or more. With 2 mg. per Kg. the central effects become pronounced, drowsiness alternating with restlessness, the latter predominating. The pupils are dilated.

Narcotic Symptoms in Lower Mammals.—The cerebral effects are almost purely depressant (analgesia, lethargy, stupor, sleep and coma) in the dog, rabbit, guinea pig, rat, mouse and also in birds. The reflexes are generally exaggerated, as also postural plasticity. Dogs sometimes react with tremors and choreiform twitchings of the limbs. The *excitability of the motor areas* to electric stimulation is not altered, even by the largest doses (Hitzig, 1875). Dogs sometimes show *delirious excitement* soon after the injection and generally do so when they awaken from the morphine sleep, as described by Claude Bernard (*Anesthésiques*, p. 508): "They are often frightened, with haggard eyes, the hind legs down and half paralyzed, which gives them the position and walk like a hyena. When one calls the dogs in this condition they run away as if frightened; they do not recognize their master and try to hide in dark places. This intellectual derangement sometimes lasts at least twelve hours."

The deliriant action is especially prominent with cats and also with the horse, ass, beef, sheep, pig and goat, but intermingled in various degrees with the lethargic and analgesic effect. Cats exhibit a violent mania, racing about as if in extreme terror, with prominent eyes, widely dilated pupils and erected hair, scratching and clawing wildly. Finally they may go into fatal epileptiform convulsions. The deliriant action is on subcortical centers, in the hypothalamus, for it occurs typically after complete removal of both cerebral hemispheres, but not if the hypothalamus is removed. Local or systemic application of morphine does not affect the reactivity of the cruciate cortex or hypothalamus of cats to faradic stimulation (J. H. Masserman; W. E. Hambourger, 1937, 1940). The excitant effect on cats is produced by codeine and thebaine, while papaverine and narceine are mainly depressant (G. H. Müller). *Dilaudid* and *demerol* are also highly excitant (D. I. Macht, 1946).

Postural Rigidity.—The morphine alkaloids may produce catatonic rigidity, acting probably through the midbrain. This may be responsible for the ataxic "floating" sensation. In rats it is plastic, so that the animals tend to preserve imposed awkward positions. In mice, even small doses produce stiff erection of the tail (Straub).

The *hyenoid posture* of dogs may belong in the same category. Morphine induces a similar position in mice if pernocton is given at the same time (S. Loewe, 1938). Morphine controls the attacks of parathyroid tetany so as to prevent death (J. H. Sloan, 1926).

Straub's Mouse Test.—White mice respond to the hypodermic injection of morphine (0.02 mg.) or its esters by a characteristic S-shaped stiff erection of the tail. The same effect is produced by other convulsants, but generally only with larger doses (Rassers, 1916), for instance by nicotine, 1 mg. per 15 Gm. mouse (Jensen and Runry, 1918). It has some medicolegal importance, as it is not produced by the putrefactive bases, tyramine, cadaverine and putrescine. Codeine is about a tenth as potent as morphine. Atropine and scopolamine inhibit the morphine phenomenon (A. Juul, 1939). It has been attributed to intense tenesmus of the anal sphincter, originating in the medulla and transmitted through the pelvic nerves (Van Leersum, 1918). Heinekamp, 1922, refers it to stimulation of the spinal cord.

Curare Action.—All members of the group, when applied directly to a muscle preparation, exert a weak and slow curare action: if the motor nerve is stimulated with a tetanizing current, the muscle responds with a series of rapid separate contractions, instead of a fused tetanus. Larger doses paralyze the muscle-nerve endings completely. Diacetylmorphine acts more powerfully than morphine or codeine, but the action is too weak to be observed in intact mammals (Hale, 1909).

Spinal Cord.—Morphine and all the members of the group increase the spinal reflexes (even in tabes—Orsnato, 1918). Large doses, in frogs, produce convulsions indistinguishable from those caused by strychnine. Mammals generally die from respiratory depression before the convulsant stage can develop; but convulsions are sometimes seen in man, when toxic doses (3 grains) are taken (A. Gordon, 1915; Keen). In dogs, the intraspinal (subarachnoid) injection of morphine produces marked convulsions (McGuigan and Ross, 1915). The convulsant action is stronger with codeine and especially with thebaine, so that this is generally placed in the strychnine group.

Cisternal injection of morphine into cats provokes marked *pruritus*, with scratching reflex. This effect is also produced by codeine and paracodeine, not by dionine or heroin. It is prevented by phenobarbital and by injection of procaine into the region of the head and neck. It is not prevented by atropine and is increased by ergotoxine (Mehes, 1938; Konigstein, 1936).

Therapeutic Uses of the Analgetic and Sedative Actions.—Morphine and opium are used mainly to attenuate pain, procure sleep, check peristalsis, suppress cough, ease dyspnea, facilitate anesthesia and secure muscular quiet. These indications arise in a great variety of diseases; and since the action of the opiates is certain and highly effective, their field of usefulness is extensive and important. They must be used with discretion, remembering that the relief is generally only symptomatic and may sometimes interfere with the natural processes of repair, or obscure the observation of the progress of the disease. The danger of addiction restricts their employment in neurotic individuals and in chronic diseases (except when these are hopeless). The danger can be somewhat diminished if the morphine is not intrusted to the patient himself, but administered only by the physician, with somewhat impressive formalities of asepsis. The side actions (constipation, nausea, gastric disturbance and occasional excitement) may also interfere with the usefulness. *Demerol* has similar effects and indications, although it is not chemically related to morphine.

Against pain and extreme physical discomfort, morphine surpasses all other analgetics in efficiency, particularly in persistent and exhausting pain, such as that of trauma, inflammation or neuralgia. The therapeutic effect involves raised threshold to pain; dissociation of pain perception from the usual reaction to pain; lethargy and sleep (H. G. Wolff, Hardy and Goodell, 1940). It is generally used to dull rather than actually to abolish the pain, to render the patient indifferent or detached from the discomfort and fag, and thus to give rest and permit sleep. It should not be used as a somnifacient except when it is needed for pain, cough or dyspnea. It should be avoided in nervous insomnia or psychic excitement. *Psychic and motor exaltations,* as in delirium tremens or atropine poisoning, are controlled only by very large doses, and are better treated by paraldehyde or barbiturates. Morphine is not very effective against the *colic pains* of smooth-muscle spasms, but gives rest between the paroxysms and amnesia; this is utilized in obstetrics "twilight sleep." In *hemorrhage* the quiet induced by morphine favors arrest of the bleeding, by keeping the blood pressure low and permitting the formation of the clot. It is especially valuable when the hemorrhage is in an inaccessible situation. The depressant effect on the respiration enjoins caution in the use of larger doses, particularly in severe hemorrhage, cardiac disease and other debilitating conditions. It does not suppress *convulsions* as do the barbiturates and the aliphatic narcotics, and indeed increases spinal excitability; but it lessens the apprehension and pain. The depressant action on the respiration must be borne in mind (Dreyfus, 1914). (Codeine does not inhibit, but rather increases the convulsions of camphor; Januschke and Masslow, 1915.)

Comparative Analgetic Efficiency.—Morphine surpasses its commonly used derivatives; but codeine often suffices, with the advantage that it has less side actions, *f. i.,* it is less nauseant and less constipative, and its clinical use only rarely leads to addiction. Dilaudid also avoids the side actions (Straud, 1934), but is not proof against addiction. This holds also for demerol. Carefully controlled clinical tests indicate that the actions of the mixture of opium alkaloids ("*Pantopon*") are indistinguishable from those of the morphine which it contains, the $\frac{1}{3}$ grain tablet of pantopon corresponding to $\frac{1}{4}$ grain of morphine sulfate in analgetic efficiency and in all the side actions. It has therefore no advantage (J. M. Hayman and Fox, 1937). The same relation holds for critical experiments in animals (Barlow, 1931).

Analgetic Dosage.—Severe acute pain requires 8 to 15 mg. ($\frac{1}{8}$ to $\frac{1}{4}$ grain) of morphine hypodermically; larger doses are usually not materially more effective unless tolerance has been acquired, and this must be carefully avoided. In lighter grades of pain, codeine should be used, 0.015 to 0.06 Gm. ($\frac{1}{4}$ to 1 grain) by mouth, preferably with 0.3 to 0.65 Gm. (5 to 10 grains) of acetylsalicylic acid. This suffices for many cases of cancer. Morphine is used more economically in chronic cases if moderate doses (10 to 15 mg.) are given by mouth at intervals of three to four hours, than with larger doses at longer intervals; but routine intervals favor addiction (E. M. Daland, 1936).

The stress and excitement involved in *battle casualties* require 30 mg., $\frac{1}{2}$ grain. This is safe, but must not be repeated until after six hours. *In shock,* 10 to 15 mg. may be injected by vein, to avoid delayed absorption. It allays pain and apprehension, although it has no direct effect on the shock.

Quantitative measurements of the *pain threshold* in man show that the analgetic effect of morphine increases markedly with the dose to 10 mg. intramuscularly; and but little more between 15 and 30 mg. With codeine, the analgesia is near its maximum at 60 mg., but increases somewhat to 120 mg. (J. D. Hardy *et al.*, 1940). The potency of pantopon is that of its morphine content. The potency of 30 mg. of morphine is equaled by 3 mg. of dilaudid or 6.6 mg. of metapon. *Addition of acetanilid,* amidopyrine or acetylsalicylic acid potentiates the morphine analgesia (Fellows and Cunningham, 1943). Sensations other than pain are not affected by therapeutic doses of morphine or codeine or other analgetics, such as acetylsalicylic acid, evipal or alcohol (Wikler *et al.*, 1945). *Neostigmine* was reported to potentiate the analgetic effects of morphine in man and in animals, perhaps by diminishing its urinary excretion (Slaughter *et al.*, 1943, 1946); but Andrews, 1942, failed to find significant potentiation. *Methods for determining analgetic potency on animals* are described by Knowlton and Gross, 1943 (electric threshold, dogs), and by D'Amour and Smith, 1941 (heat on rat tails). The results agree with the clinical.

Local application of opiates to bruises, etc., is not rational, for morphine has practically no action on the sensory endings or on the peripheral sensory nerves. A weak local analgesic effect was reported by Macht, Johnson and Ballinger, 1916, and confirmed by Sollmann, 1917 (endermic method). This, however, is so slight, brief and superficial that it is doubtful whether it has any part in the therapeutic analgesia. Practically, the site of application is no more affected than other regions of the body (Jolly and Hilsmann, 1874). Any apparent success is largely imaginary; although there may be some central analgesia, since morphine is readily absorbed from wounds and mucous membranes and to a slight extent even from the unbroken skin. With the antiquated "Lead and Opium Wash," the precipitate formed by the lead with the gums and meconic acid furnishes a soothing protection. The morphine is not precipitated by the lead.

For Pre-Anesthetic Sedation.—Morphine, 10 mg. or $\frac{1}{6}$ grain hypodermically half an hour before inhalation anesthesia, lessens apprehension and gives a smoother anesthesia, with a smaller quantity of the anesthetic agents, diminishes the discomfort on awakening and reinforces the postanesthetic sleep. It is often used in conjunction with barbiturates or avertin to build up a "basal anesthesia," to be completed by a relatively small amount of inhalation anesthetic. It is *synergistic with pentothal* and may produce deep coma unless proper allowance is made in the dosage (S. L. Lieberman, 1945). It is used with scopolamine (see Index) for "twilight sleep" in obstetrics. Its use involves a tendency to respiratory depression, which must be watched. Morphine is similarly used in connection with local anesthesia, to allay nervousness and distract attention. Codeine is considerably less effective for preanesthetic medication. Experimental data on the relative efficiency of preanesthetic medication are given by O. W. Barlow and Stormont, 1932, and Barlow and Duncan, 1933.

Sedative Action in Cough.—The morphine alkaloids check cough chiefly by diminishing attention to the irritative reflex. They also decrease the quantity of bronchial secretion, partly by a direct action (Rossbach, 1882) probably central, and partly by the drying of the mucus as it stays longer in the air passages. Opiates as "sedative expectorants" in bronchitis and phthisis are useful when the cough is mainly irritative; and contraindicated when required for the expulsion of excessive mucus. Even then, however, they may be needed to secure sleep. Small doses suffice, and *codeine,* 10 to 30 mg. ($\frac{1}{6}$ to $\frac{1}{2}$ grain) orally, should be preferred. The average patient obtains relief from 10 mg. every four hours (L. F. Davenport, 1938). The anti-tussive dosage of morphine is 2 to 5 mg. ($\frac{1}{30}$ to $\frac{1}{12}$ grain); Tr. Opii $\frac{1}{2}$ cc. or 10 drops; dionin, 15 mg. or $\frac{1}{4}$ grain; heroin, 5 mg. or $\frac{1}{12}$ grain.

Heroin is effective, but has no material advantage. It is extraordinarily addicting and much more toxic than morphine (Harnack, 1899).

Respiration.—Small and moderate (non-narcotic) doses of morphine (3 to 15 mg. in man) quiet the respiration. The rate is generally moderately slowed (Gscheidlen, 1869), markedly so if it had been rapid; the depth is often rather increased, especially if it had been shallow; the minute volume is usually somewhat decreased, but may be unaltered or even increased; the response to carbon dioxide and asphyxia is greatly diminished. Spasmodic irregularities, dyspneas and air hunger are removed or allayed. The regular deep respiration thus induced is more favorable to air exchange, so that the respiration is more efficient even when it is slower. *Toxic doses* produce progressively serious depression of the respiratory center: marked decrease of excitability, rate, depth and efficiency; periodic respiration (Filehne; Barbour, 1914) resembling the "Cheyne-Stokes type" (but probably not typically so; Krongliakoff-Blanc, 1928), and finally arrest of respiration, before the heart is seriously injured.

The mechanism of the respiratory depression is presumably analogous to the psychic effects, *i. e.,* inattention to the stimuli that normally influence and entertain respiration. This would be most marked toward persistent stimuli, such as those of cough and carbon dioxide; while the response to abrupt stimulation, for instance of the sciatic nerve, may even be increased (S. J. Cohen and McGuigan, 1924). With toxic doses, the apathy would gradually abolish all respiration. In habituation, the organism learns to adapt its indispensable functions to the apathy, and the toxicity is greatly diminished. Different degrees of apathy would explain the wide variations in the fatal dose for different animals.

Relation to Dosage.—With dogs and rabbits, Macht, 1915, found that small doses (0.1 mg. per Kg.) markedly slowed the rate, but somewhat increased the minute volume and alveolar ventilation; but the response of the center to CO_2 was somewhat decreased. Full doses (1 to 5 mg. per Kg.) diminished the rate, minute volume alveolar ventilation and response to CO_2.

Quickening of respiration is seen occasionally with therapeutic doses in man (Higgins and Means, 1915) and occurs at certain stages in animals: *in the dog,* the hypodermic injection of morphine first causes quickening of respiration (perhaps through nausea) followed in fifteen minutes by the typical slowing (Mayor, 1908). In *frogs*, the slowing is succeeded by quickening, just prior to the convulsive stage. A *secondary quickening* is also seen in rabbits (Filehne, 1879; Cerna, 1892) but never in man.

Diminished Sensibility to Asphyxia.—In normal animals, excess of carbon dioxide and deficiency of oxygen increase the depth and rate of respiration. Morphine dulls this response (A. Loewy, 1890; Cushny and Lieb, 1915); apnea is easily produced and very persistent (Filehne, 1879); the blood becomes very venous (Filehne and Kionka, 1895). Schmidt, 1924, attributes the diminished response to CO_2 to slowing of active expiration. The average concentration of blood at high altitudes is not altered by 15 mg. of morphine (E. W. Peterson *et al.*, 1945).

Respiratory Reflexes.—The effects of morphine vary for the different reflexes. In general, it tends to increase the sensibility to inhibitory and spinal reflexes, and has little effect on acute augmentory reflexes (Cushny, 1913; Cohen and McGuigan, 1924).

Other Opium Alkaloids on the Respiration.—The effects of the morphine derivatives, codeine, heroin, dionine, etc., are essentially the same as those of morphine (Issekutz, 1911). In rabbits and rats respiratory depresssion equivalent to that of morphine requires about double the dosage for pantopon, four times for codeine, four to eight times for narcotine, seven times for papaverine (Barlow, 1933), seventeen times for dilaudid (C. J. Wright and Barbour, 1934). Barbiturates (especially those with lasting action) potentiate the respiratory depression more than avertin, chloral or urethane (Maloney and Tatum, 1930). *Diacetyl-morphine (Heroin)* was introduced by Dreser, 1898, with the claim that therapeutic doses lessen the cough reflex and slow the respiration; but that the inspirations are deepened and more powerful, so that the alveolar air is more effectively ventilated. Independent workers have shown that there is no real difference from morphine (Fraenkel, Harnack, Lewandowsky, Santesson, Winternitz, 1899; Issekutz, 1911; Cushny, 1913). In man, the respiratory effects of 5 mg. of heroin correspond almost quantitatively to those of 15 mg. of morphine (Higgins and Means, 1915). *N-allyl normorphine* and the corresponding codeine compound stimulate respiration and antagonize the morphine depression (E. R. Hart, 1943). *The alkaloids of the papaverine group* generally stimulate the respiratory center, so that opium is rather less depressant to the respiration than would be expected from its morphine content (Macht, 1915).

Use in Asthma and Dyspnea.—Morphine (15 mg. or $\frac{1}{4}$ grain, hypodermically) may relieve, by quieting the patient and allaying the "air hunger" and anxiety. It may even improve the efficiency of the respiration, rendering shallow breathing deeper, and convulsive respiration regular. It is likely to become dangerous, however, by suppressing the effort to drive the air through the narrowed passage (Balyeat, 1939). Morphine should be avoided in bronchial asthma, for fear of habit-formation. It might also lead to addiction in cardiac dyspnea. It is useful in acute respiratory disease, for instance pneumonia or pleurisy; deleterious depression need scarcely be feared from therapeutic doses.

Morphine in "Gassing" by Chlorine and Other Volatile Irritants.—Morphine not only dulls the agonizing "air hunger," but tends to save life by quieting the patient and thus diminishing the use of oxygen and the production of carbon dioxide. Hjort and Taylor, 1919, claim that it also prolongs the maintenance of alkali reserve.

Bronchial muscles are slightly relaxed by small therapeutic doses of morphine, and more powerfully by papaverine and narcotine (Pal, 1913; Macht, 1915); large doses of morphine, codeine, dionine, and especially heroin, narcotine and thebaine, produce marked constriction. Higgins and Means, 1915, observed bronchial constriction in man with 15 mg. of morphine or 5 mg. of heroin. The relaxation may play a part in the relief of bronchial spasm (*asthma*); while the constriction may contribute to the asphyxia of toxic doses.

The effects are peripheral, for they occur on excised bronchial muscle (relaxation, Trendelenburg, 1912) as well as in pithed (constriction, Jackson, 1916) and in intact animals (relaxation with small, constriction with large doses; Brodie and Dixon, 1903). The constrictor action is not antagonized by atropine or ergotamine. It can be overcome by powerful dilator (sympathetic) stimulation, epinephrine, hordenine, cocaine (Swanson, 1929).

Autonomic System.—The peripheral effects of morphine are complicated by its inhibitory action on choline esterase, resulting in cholinergic stimulation; and by increased output of epinephrine with resultant adrenergic stimulation.

Choline esterase inactivation by morphine was demonstrated by Bernheim and Bernheim, 1936, and studied by G. S. Eadie, 1941. Analogous effects of morphine esters and derivatives are described by C. I. Wright and Sabine, 1943.

Iris.—In man (not generally in animals) even small, scarcely analgetic doses of morphine constrict the pupils, and toxic doses result in pin-point miosis. This has diagnostic importance. The action is central, for it does not occur on local application or in excised eyes. It is due to a stronger constrictor (oculomotor) tone, for it disappears when the oculomotor endings are paralyzed by atropine. It is somewhat diminished by section of the sympathetic supply (Amsler, 1927). The miosis appears analogous to that of sleep or of general anesthesia, namely, extinction of the centripetal sensory impulses which in the waking state restrain the tonus of the oculomotor center (Meyer and Gottlieb). It requires intactness of the optic nerve (McCrea *et al.*, 1942). Morphine also produces a fairly lasting rise of intra-ocular pressure (Myashita, 1913). The rise is shorter with ethyl-morphine.

Pupil Changes in Animals.—In *cats*, the pupils are dilated by morphine in conformity with the inhibition of the oculomotor tone by the psychic excitement. Dilaudid and demerol also produce maximal mydriasis in cats. Codeine and papaverine do not change the pupil (D. I. Macht, 1946). The pupils of morphinized *dogs* are contracted with internal strabismus, during the sleep, but if they are wakened the pupils dilate and the strabismus disappears (C. Bernard). *In albino rats* morphine produces no perceptible change in the pupil, but greatly increases the mydriatic response to sympathetic stimulants, cocaine, epinephrine, ephedrine (Koppanyi, 1932).

Circulation.—Therapeutic doses of morphine or its derivatives do not affect the circulation materially. In man, there is generally an (indirect) increase of *pulse rate* immediately after an injection; this is quickly followed by persistent moderate slowing, with increased fulness and force (stimulation of vagus center). The blood pressure, after a short rise, may remain level (Anderes, 1913), or falls slightly (Guinard, 1895), through the slowing, and perhaps through incipient depression of the vasomotor center. The cutaneous vessels are markedly flushed, and sometimes also those of the oral mucous membrane and conjunctiva. With *toxic doses,* fall of blood pressure is more marked (central vasomotor depression) and the pulse becomes weak, varying in rate, and often arrhythmic (stimulation of vagus center and disturbed cardiac conduction). The heart muscle suffers indirectly, by the low blood pressure and asphyxia (hence danger in cardiac insufficiency, especially when combined with dyspnea). Ordinarily the circulation remains fairly good, until death occurs by paralysis of respiration. Direct depression of the heart is produced only when morphine, or especially its derivatives, are perfused directly through the heart. Hering, 1915, believes that the increased vagus tone resulting from large doses may indirectly produce ventricular automatism, or even fibrillation, especially in pathologic hearts tending in that direction.

Vagus Center and Cardiac Conduction.—Dogs show the above phenomena in more marked degree. The preliminary acceleration is due to nausea. The typical slowing is not seen after section of the vagi, and is therefore central. It occurs with small doses, increases with larger doses and passes into arrhythmia (van Egmond, 1911; Anderes, 1913); and sino-auricular and auriculo-ventricular heart block, separate or combined, removable by atropine (Eyster and Meek, 1913). The reflex excitability of the vagus center is also increased (Jackson and Ewing, 1914). The action is probably on the medulla, not on the cerebrum (B. H. Robbins *et al.*, 1939). Electrocardiograms also show central vagus stimulation (Cohen, 1913). The effect on the pulse rate is inconstant in cats, absent in rabbits (Egmond). Anderes found constant slowing in rabbits, the vagus stimulation being partly central, partly peripheral through decrease of the negative thoracic pressure. Morphine sensitizes the vagus center to epinephrine (Heinekamp, 1919). The cardio-inhibitory center of the turtle is stimulated by perfusing morphine through the medullary circulation (Bush, 1920).

Cardio-inhibitory reflexes from the carotid sinus and aortic arch are intensified by morphine, in dogs (Van der Linden, 1932). Hering and Koch, 1931, concluded that the ordinary morphine bradycardia is due to this cause; but Heyman *et al.*, 1931, found that it occurs also after denervation of these zones, so that morphine must stimulate the inhibitory center directly.

Blood pressure fall on intravenous injection occurs with doses of 1 mg. or more per Kg. in dogs and cats, not in rabbits, rats or guinea pigs. Tolerance is rapidly acquired (C. F. Schmidt and Livingston, 1933). It is perhaps a "flocculation shock."

Cardiac Muscle.—Morphine and all its derivatives first increase the rate and amplitude of perfused *mammalian heart.* This is followed by decrease and finally systolic standstill (Gruber and Robinson, 1929). The rate of the perfused atropinized *frog's heart* is quickened by dilute, slowed by more concentrated solutions of all the papaveraceous alkaloids, morphine being the least deleterious (Hale, 1909). The refractory phase is prolonged by morphine (Junkmann, 1925). Lippins, 1908, found peronine highly toxic for the turtle's heart. Narcotine is the most toxic of the opium alkaloids, for the heart (Macht, 1915). Papaverine lowers the cardiac tone (Pal); this is followed by considerable tachycardia (Rennon and Desbouis, 1914). The *tonus waves of turtle's auricles* are augmented by morphine, depressed by papaverine and benzyl alcohol (C. D. Snyder and Andrus, 1919). The *cardiac ganglia* show degenerative histologic lesions, similar to those of alcohol or chloroform (Lissauer, 1914). Gscheidlen, 1869, found that the *vasomotor endings* were not completely paralyzed even in advanced poisoning; stimulation of the spinal cord still gives a rise. The venous *pressure* is not changed by moderate doses, and is slightly lowered by toxic doses, indicating vasodilation (Capps and Matthews, 1913). The *coronary circulation* is quickened by dilatation of the coronary vessels, by most of the opium alkaloids. The action is most marked with narcotine and papaverine, slight with morphine, very slight with codeine, heroin or pantopon, and absent with narceine and thebaine (Macht, 1915; Gruber and Robinson, 1929).

Cerebral Circulation.—The effects are small and inconstant with ordinary doses (Aliprandi, 1905). Frankfurther and Hirschfeld, 1910, describe an initial increase of brain volume, followed by decrease, the latter probably due to the fall in general blood pressure.

Action on Skin, Diaphoresis, Use against Colds.—Morphine and its esters have a direct mild irritant action on the skin, resulting in erythema, itching and wheals. These effects are especially marked with local application to the scarified skin, but the internal administration of therapeutic doses produces flushing (extending also to the oral mucosa, Claude Bernard), a sensation of comfortable warmth and diaphoresis; sometimes skin rashes in the over-susceptible. With toxic doses the skin becomes pale (splanchnic vasodilatation) and cyanotic (asphyxia). The diaphoretic action is used to treat and perhaps abort incipient colds, preferably as codeine (30 mg., ½ grain, in morning and afternoon, and double this dosage at night, for not more than two days). The addition of papaverine has been patented, but its usefulness is questionable. "Dover's powder" (Pulvis Ipecacuanhae et Opii), 0.5 Gm., was formerly used for this purpose.

Wheals.—The local application of solutions of morphine or any of its esters to the scarified skin results in the production of an urticarial wheal (Philippson, 1899; Toisk and Hari, 1903; Jadassohn and Rothe, 1914; Sollmann, 1917). Contact dermatitis in personnel manufacturing morphine has been reported (Brit. J. Derm. and Syph., 1944, *56*:151). Similar wheals are produced by histamine, peptone, emetine and calcium chloride (Sollmann and Pilcher, 1917). The susceptibility to wheal formation is the same in addicts as in normal individuals; so that tolerance is not acquired by habituation (Pilcher and Sollmann, 1923). This wheal formation is responsible for the itching and probably for the sneezing that are sometimes noted in morphine poisoning. The pruritus was described by the Greeks, but seems to have been forgotten until quite recently (Francis Adams, 1830; Edinbrgh. Med. and Surg. Jour., *1*:315).

Conjunctival Reaction to Ethylmorphine (Dionin).—The direct application of a 1 to 5 per cent solution or ointment produces burning pain, hyperemia, and then acute edema of the lids and conjunctiva (chemosis), with prolonged analgesia. The edema is absorbed without ill effects. This reaction is used in ophthalmology for analgesia and treatment in conjunctivitis, corneal ulcer, acute glaucoma, iritis and other inflammatory conditions of the uveal tract.

The edema appears in a few minutes and lasts for several hours. There is some local anesthesia. The pupils are at first constricted, and the intra-ocular tension is raised (Toczyski, 1912). The edema does not occur in rabbits, but readily in dogs or cats (Axenfeld, 1905). Benzol-morphine (peronine) is said to act in the same way; but the effect does not occur with morphine, codeine, heroin or any of the natural opium alkaloids.

Suppression of Saliva.—Therapeutic doses of morphine produce dryness of the mouth, and thirst, by abolishing the reflex secretion of saliva. Claude Bernard showed on dogs that it does not hinder secretion on peripheral stimulation of the chorda tympani nerves, but suppresses the reflex secretion of placing acid in the mouth, or of stimulation of the central end of the divided lingual nerve. The action is therefore central (V. E. Henderson, 1910).

Nauseant and Emetic Action.—Morphine tends to produce nausea and vomiting. The appetite is diminished through the lesser perception of hunger and through the gastric derangement. The effect is independent of the mode of administration, the action being central. The severity varies in different individuals; in some cases it is so serious, and accompanied by so much depression, as to preclude the use of the drug. It may sometimes be diminished by bromide or by atropine (I. Simon, 1907). Codeine is distinctly less nauseant than morphine. The action of the mixed opium alkaloids (pantopon, etc.) appears to correspond essentially to their morphine content (Hayman and Fox, 1937).

Site of the Emetic Action.—This is essentially central; for it occurs when all afferent impulses from the digestive tract are excluded; and it is also evoked when small quantities of morphine or acetylmorphine are applied directly to the floor of the fourth ventricle (Hatcher and Weiss, 1923). It may conceivably be aided by reflexes from the gastric spasm; for atropine appears to diminish the emetic tendency. There is no evidence of local gastric irritation. Vomiting occurs more readily with hypodermic than with intravenous injection; probably because the latter depresses the vomiting center too rapidly. *Nausea salivation* is profuse in dogs. Repeated injections establish a strong conditioned salivation reflex, which does not diminish as the habituation progresses but rather increases with the dosage. (Pilocarpine does not establish a conditioned reflex and inhibits that of morphine; Krylov, 1930.)

Antiemetic Action.—With large doses of the morphine alkaloids, the emesis is followed by diminished susceptibility to vomiting. This action is also mainly central (Leake, 1922). Morphine is prescribed against vomiting, but the doses which can be safely prescribed are often ineffective.

Dogs, after the primary emesis, do not respond to irritant emetics or apomorphine, probably because of depression of the vomiting center, although morphine, codeine or heroin are antemetic in doses which are not narcotic, while chloral or urethane, to prevent vomiting, must be exhibited to full narcotic action (Ruth, 1913). Contracture of the cardial sphincter, which was postulated by Magnus, 1908, may prevent the emptying of the stomach, but would not arrest emetic movements (Hatcher). Papaverine is not antemetic (Ruth).

Gastric Tonus and Sojourn of Food.—Morphine causes prolonged spastic contraction of the prepyloric and pyloric sphincters, delaying the passage of food through the stomach to five and a half hours (Gordonoff, 1925), which correspondingly defers absorption (*f. i.*, of iodide; Baas, 1904). This plays a part in the constipating action of morphine.

These actions have been confirmed by roentgen examination and by examination of stomach contents, in man as well as in animals (Magnus, 1906; Gruber, Thomas *et al.*, 1936; Veach, 1937; review, H. Krueger, 1937). Similar results were obtained by transfusion *in situ;* papaverine relieved the spasm (H. Schroeder, 1933). Discordant results were reported by Plant and Miller, 1928, for gastric fistulas.

Gastric Secretion.—In fasting human subjects, morphine (0.01 Gm. hypodermically) decreases gastric secretion, the volume being diminished more than the acidity. The decrease seems parallel to the mental depression, being least marked or absent if the subject becomes talkative or excited. The inhibition is easily overcome by stimulation, such as the sight of food, and by histamine (K. C. Wang *et al.*, 1936). The decrease is greater in normal than in habituated animals (P. Ellinger and Seeger, 1934).

Several observers have reported increase of secretion by morphine in fasting animals (Chiari, 1915; Smirnow and Schirokij, 1927). In dogs with a Pavlov stomach, Riegel, 1900, obtained first a decrease, then an increase of volume and acidity. Claude Bernard reported that digestion in the pigeon's crop was arrested by morphine when injected into the crop, but not on hypodermic injection, indicating a local action. *Pancreatic secretion* is decreased by morphine, as is also the response to secretin (O. Cohnheim and Modrakowski, 1911).

Constipative Action.—Morphine produces constipation, even with small doses, delaying the passage of the contents through every part of the digestive tract, chiefly by spastic contracture of the gastric sphincters, and through decreased propulsive efficiency by tonic spasticity of the intestinal musculature. The action is directly on the muscle and persists also in habituated individuals. It is an undesirable side effect of its analgetic use, but is valuable for arresting diarrheas and for quieting peristalsis in acute inflammations of the intestines and peritoneum. In acute intestinal catarrh, if the intestines are first cleared of toxic and irritant material by a cathartic, the rest afforded by opiates favors the subsidence of the inflammation. Tincture of opium by mouth (0.5 cc. or 10 drops) or a teaspoonful of paregoric deserves preference. Opium is only moderately effective in the colic of lead poisoning. In peritonitis it relieves the pain, both directly and by lessening peristalsis; but the disguise of the symptoms may be surgically objectionable. In biliary and renal colic, morphine (15 mg. or $\frac{1}{4}$ grain) is given hypodermically, to lessen the suffering (usually with 1 mg. of atropine to relax the ducts).

Codeine, dilaudid and acetylmorphine (heroin) produce qualitatively identical effects, both on the stomach and on the intestines; codeine and dilaudid being considerably weaker, and heroin somewhat stronger, than morphine (Plant and Miller, 1923). Mixtures of the alkaloids give simple summation (Gordonoff, 1925). Opium as a whole is therefore somewhat more constipating than would correspond to its morphine content (Zunz, 1921). Papaverine and the other isoquinoline alkaloids do not cause gastric spasm. They depress the intestinal tone, but their action is evidently overcome by the morphine.

The relative delay at various levels of the digestive tract varies with conditions, such as the degree of distention and the presence of irritation, in each of the regions. *In normal man,* Zehbe, 1913, found the total time of passage through the digestive tract nearly doubled by morphine. The chief delay was in the colon and rectum; the gastric and intestinal passages were each lengthened by a third. Pancoast and Hopkins, 1915, reported the delay as chiefly in the small intestines and but little in the colon. If morphine is administered with the test meal, the delay is confined largely to the stomach, because the food does not enter the intestines until the effects of the morphine have practically passed off (Gordonoff, 1925). E. H. Fell, 1938, found no characteristic delay in the emptying time of the stomach and small intestines, but the emptying of the colon was delayed by eight to thirty-one hours and the total sojourn in the intestines by four to twenty-four hours. He attributes the constipation to the difficulty of expelling the hard, dry feces against the increased tonus of the anal sphincters.

In dogs, M. Krueger, 1937 (review), found that 6 mg. of morphine per Kg. delay the evacuation of feces about twenty-four hours, distributed about as follows: *sojourn in stomach,* thirteen hours, chiefly by closure of the pylorus and constriction of the prepyloric sphincter; *sojourn in small intestines,* seven hours, chiefly by decrease of biliary and pancreatic secretion, decrease of propulsive activity, increased viscosity of contents; *sojourn in colon,* four hours, chiefly by drying of contents, difficulty of passing through the contracted sphincter.

Historical.—The mechanism of the morphine constipation has been much disputed (the bibliography of Uhlmann and Abelin, 1920, cites 314 titles) chiefly because the quieting of peristalsis was supposed to require depression of the intestines. The older workers (reviewed by Magnus, 1910) assumed depression of the local reflex which was assigned to the plexuses of Auerbach and Meissner, or central stimulation of the inhibitory splanchnic fibers (Nothnagel, 1882). This postulated depression could not be confirmed; the constipative action occurs after section of the intestinal nerves and after atropine; and excised intestines show chiefly stimulation. The explanation of spastic arrest did not readily suggest itself, because other spastic agents generally pass through a stage of increased peristalsis and colic, which is absent with morphine. The cause of this peculiar difference is not known. The credit for demonstrating the importance of the intestinal spasticity belongs to Plant and Miller, 1923, 1925.

Antagonism to Cathartics.—Magnus, 1906, 1908, found that the constipative action in the milk diarrhea of cats is due almost entirely to the gastric action. The diarrheas of senna, castor oil and magnesia were resistant to morphine; but the inflammatory diarrhea of colocynth was arrested by a direct intestinal action (Padtberg, 1911). Later experiments on animals with permanent fistulas of the small intestines show that morphine arrests the powerful peristaltic waves induced by the emodin cathartics and by podophyllin, converting them into the spastic tonus (C. M. Gruber, Bryan and Richardson, 1931). Morphine and codeine also increase the tonus of exposed intestine when it has been depressed by magnesium sulfate (N. B. Dreyer, 1929). *Papaverine* and the chemically related chelidonium alkaloids are depressant to the intestinal movements, and relax the colic of acetylcholine and pilocarpine, and of phenoplhthalein, podophyllin and senna (L. Alkan, 1928).

Tonicity of Small Intestines.—Various methods of observation show that intestinal muscle shortens and develops increased tension, more prolonged contraction phase with slowing of the rhythm (to a fourth; Krueger and Samwalt, 1936), and marked slowing of propulsion. The spasticity may be observed in man through the thin skin of herniae (Plant and Miller, 1925), and by intubation; in animals by pressure changes in permanent fistulas (Plant and Miller); by propulsion of a bolus in an intestinal loop; and by artificial abdominal windows (Gordonoff, 1925). It occurs also in excised intestines, both with perfused lumen (Baur, 1925) and with Magnus segments (references, Uhlenhuth and Abelin, 1920). It is not prevented by atropine; the action is therefore entirely peripheral (review, Krueger, 1937).

Intubation studies on human small intestine permit observation under clinical conditions. Hypodermic injection of 10 to 30 mg. of morphine produces within a few minutes tonic contraction of the duodenum practically obliterating the lumen, followed by dilation lasting several hours. The ileum shows marked decrease of the contraction waves, with slow rise of tonus, and later, stationary tonus rings. The effects were detectable for three days (W. O. Abbott and Pendergrass, 1936). In an externalized loop of the lower ileum, in man, 8 mg. of morphine caused decrease in propulsive activity, more frequent mixing waves and, often, an increase of tonus (A. C. Forster, 1938).

Pressure Changes in Unanesthetized Dogs with Thiry-Vella Fistulas.—Plant and Miller, 1923, first showed the stationary tonus effect by this method. The rate of the contractions is slowed and the amplitude may be increased. Large doses abolish peristaltic activity. Repeated intravenous injections decrease the general tonus and may increase the force of the contractions (Gruber *et al.*, 1929 and 1932, and H. Krueger *et al.*, 1934 and 1938). The *progress of a bolus* through the Thiry-Vella loop gives truer information as to propulsion than does the balloon pressure. In the ileum and jejunum of unanesthetized dogs, morphine briefly augments the propulsive activity, but this is followed by high tonus with marked and prolonged slowing or arrest of propulsion (J. P. Quigley, Highstone and Ivy, 1934; Weisel *et al.*, 1938; papaverine and atropine also decrease propulsion; pitressin and pitocin usually slow it; pilocarpine has little effect). The *derivatives of morphine*, natural and synthetic, act qualitatively alike, but codeine produces less tonus increase than morphine in equivalent dosage, and dilaudid still less (Krueger and Hoover, 1934). *Papaverine* depresses the tonus, but sometimes increases the tonus waves (Gruber and Robinson, 1929). On segments of excised intestines, dilaudid acts like morphine, increasing the tonus for the cat and relaxing it for guinea pigs (Gruber, Brundage *et al.*, 1935). *Physostigmine* partly potentiates the morphine action on the intestine (Slaughter and Gross, 1940).

Colon.—By the fistula and the balloon method Plant and Miller, 1928, observed that morphine produced increase of tonus and spastic contractions, during which peristalsis was abolished. These effects lasted much longer than the central narcosis. Roentgenologic observations on cats showed that morphine rendered the normal deep segmenting peristaltic contractions very shallow (Schwenter, 1912). The rectal tonus is increased in cats; this is followed by relaxation in several hours (G. N. Myers, 1940). The *anal spincter* is also contracted (Koppanyi and Murphy, 1933).

Defecation Reflex.—In addition to the muscular action, the morphine apathy diminishes the attention to the rectal sensations and therefore the responsiveness to the defecation reflex (Schapiro, 1913; Mahlo, 1913). It furnishes prompt relief to the tenesmus of diarrhea.

Purgative Action in Dogs.—Morphine increases the motility and tonus of the colon, with strong propulsive movements. Atropine prevents the propulsion but does not inhibit the tonus and nonpropulsive motility (A. F. Adler and Ivy, 1940). Hypodermic injection of large doses of morphine is generally followed by defecation. Intravenous injection of morphine, codeine, heroin (or ergotamine) causes prompt straining and defecation, through central action, for the effect does not occur if the floor of the fourth ventricle has been injured (Theo. Koppanyi, 1932).

Bile Flow.—Therapeutic doses of morphine (10 mg. hypodermically) diminish the flow of bile (Paven *et al.*, 1929) through spasm of Oddi's sphincter (Reach, 1914). After removal of the gallbladder this may raise the pressure in the common bile duct sufficiently to produce biliary colic. It may be relieved by nitrites. Papaverine has no effect (W. Walters *et al.*, 1937). Lieb and McWhorter, 1915, state that the musculature of the gallbladder is not affected; but Macht, 1917, claims that the gallbladder reacts to the opium alkaloids like the ureter, *i. e.*, that it is stimulated by morphine, depressed by papaverine. The *secretion of bile* is greatly decreased by heroin, but not by morphine (Balteceano and Vasilu, 1935).

Uterine contractions are little affected by morphine, in either direction, in clinical labor (Dodek, 1932) and in gravid and nonpregnant animals (D. Slaughter and Gross, 1937). Labor may be somewhat slowed and prolonged (Bourne and Burn, 1930) by failure to reinforce the labor pains with voluntary contractions of the abdominal muscles (Barbour and Copenhaver, 1915). The chief danger in the use of morphine is depression of the respiratory center of the child, and it should not be employed after the first stage of labor (see under *Scopolamine*).

It has been observed in rabbits that the prolonged labor tends to injure the fetus, resulting in a high ratio of still-births. This is not due to poisoning of the fetus, for it survives if removed by hysterectomy (F. F. Snyder and Lim, 1941).

Ureter.—Morphine and the derived alkaloids (including dilaudid, but to a less degree) increase the tonus of the ureter and the rate and force of its contractions (Gruber, 1936). This may conceivably interfere with their use in ureteral colic. *Papaverine* depresses the ureteral tonus and contractions (Macht, 1916), but it has not proved effective against colic.

Urinary Bladder.—Toxic doses of morphine produce spasm of the vesical sphincter, leading to distention of the bladder and constant but ineffective desire to micturate. This sometimes occurs in the therapeutic use (Czapek and Wassermann, 1914). It is diminished by habituation (Ikoma, 1924).

In guinea pigs the distention may rupture the bladder (Tappeiner, 1899). The effect is apparently the result of a depression of a detrusor center in the sacral cord, which produces reflexly a reciprocal spasm of the sphincter. Larger doses inhibit the bladder tonus (Hirano, 1938).

The other phenanthrene alkaloids also cause powerful contraction on intravenous injection in dogs (D. E. Jackson, 1916). Larger intravenous doses are inhibiting in rabbits (Hirano, 1938). The isoquinoline alkaloids (papaverine) relax (Macht, 1918). The capacity of the bladder in unanesthetized dogs is decreased by morphine, mecholyl and atropine, increased by ephedrine (Winters, 1940).

The *seminal ducts* react like the ureter (Macht, 1916). The *retractor penis* muscle of the dog is stimulated by morphine (Edmunds, 1920).

The **urine output** is diminished by morphine, clinically and in animals, including diminished response to water administration (Klemt, 1934). The chloride and nitrogen excretions are not changed except in so far as morphine may diminish food consumption. The decrease of urine volume is due to the diaphoresis; but the inhibition of water diuresis is apparently affected through liberation of antidiuretic hormone from the hypophysis, for it does not occur after destruction of the neurohypophysis (de Bodo, 1944). Morphine also hinders the transfer of injected saline solution from the blood to the tissues (Bogert, Underhill and Mendel, 1916).

Temperature.—Toxic doses of morphine lower the temperature below normal, chiefly by diminished heat production. Small doses are somewhat antipyretic by the diaphoresis.

The fall (which is sometimes preceded by a slight rise, especially in cats and guinea pigs; Helfrick, 1935) may be 2° C. with large doses. The cooling is particularly great if the animal is kept in cold surroundings. With small doses, the fall may be explained by increased heat loss from cutaneous vasodilatation; but with large doses it is due mainly to diminished heat production and finally to circulatory collapse. The heat production may be reduced by 80 per cent in extreme cases, reaching its minimum in the third hour. The heat loss is diminished (up to 20 per cent), partly through the effort of the heat centers to compensate for the diminished production, partly through the depressed circulation (Reichert, 1901).

Malaria.—Opium gives symptomatic relief, but has no curative or prophylactic value; nor does narcotine affect the parasites of any of the malarias in the peripheral blood (Chopra and Knowles, 1930).

Protozoa.—The papaverine group is toxic to these organisms, whereas the morphine group is relatively ineffective (Bills and Macht, 1924). Trypanosoma brucei is killed *in vitro* by both groups, but especially by the papaverine group. *In vivo* (rats) both groups are ineffective (Macht and Weiner, 1918). The amebicidal action of emetine, which is also an isoquinoline derivative, prompted Pick and Wasicky, 1915, to suggest the trial of papaverine against *amebic dysentery;* but it has not been successful.

Leukocytes are diminished in acute and chronic morphine poisoning (Cloetta, 1903). The injection of morphine inhibits the migration of leukocytes in inflamed frog's mesentery (Ikeda, 1916). Morphine also diminishes phagocytosis *in vitro* (Arkin, 1913); but the concentrations are different from those obtaining clinically.

Tissue Cultures.—Morphine has unfavorable effects (Kamon, 1928).

Basal Metabolism.—Morphine, even in ordinary clinical doses (H. H. Anderson, 1929), diminishes the oxygen consumption and the CO_2 output, as the result of the muscular quiet. This tends to disappear in habituation (Schoen, 1924). Cats which are excited by morphine show increased CO_2 output (Boeck and Bauer, 1874), as do other animals with the more stimulant morphine derivatives. With *codeine*, the oxygen consumption is decreased by small doses, increased by larger doses; some of the codeine derivatives produce only increase (Eddy, 1933).

Acidosis.—Large doses of morphine diminish the sensitivity of the respiratory center, increase the CO_2 content of the plasma and produce asphyxial acidosis, with marked and rapid decrease of the alkali reserve and of the *p*H of the blood. The lactic acid of the plasma is not increased (Rakieten *et al.*, 1934). Smaller doses (10 mg. per Kg. for dogs) appear to increase the alkali reserve for several hours (Hjort and Taylor, 1919). The *urine* becomes strongly alkaline, by the excretion of carbonate, after narcotic doses in dogs; rabbits' urine does not show any change of reaction (Underhill *et al.*, 1917).

Morphine Hyperglycemia.—After large doses of morphine, the *urine* often contains *reducing substances*, partly morphine-glycuronic acid (P. Mayer, 1899), partly dextrose from the asphyxia.

Clinical doses raise the blood sugar level for some hours in 10 to 15 per cent of fasting individuals. This response disappears in a few weeks if the administration is continued (Bahler, 1930). In dogs, the hypodermic injection of 10 mg. per Kg. increases the blood sugar, on the average, by 60 per cent in one-half hour and 77 per cent in one and one-half hours (E. L. Ross, 1918). A peculiar reducing substance in human urine is described by Spitta, 1908. The morphine hyperglycemia is much greater after partial destruction of the pancreas (Auer and Kleiner, 1917). *Insulin* lowers the blood sugar level as much as in other hyperglycemias (Stewart and Rogoff, 1923). *The mechanism of the hyperglycemia* appears to be a stimulation of autonomic centers which involve areas of the posterior hypothalamus. Decerebration through a midcollicular region, performed twelve to twenty-four hours previously, prevents morphine hyperglycemia and excitement in cats (C. M. Brooks, Goodwin and Willard, 1941).

Relation to Adrenals.—Morphine hyperglycemia differs essentially from asphyxial, piqûre and ether hyperglycemia in that the reaction to morphine is decidedly less if the adrenal glands have been removed or if epinephrine liberation is prevented; while this does not affect the other hyperglycemias (Stewart and Rogoff, 1922; Bodo *et al.*, 1937; Houssay and Lewis).

Antiglycemic Action.—The opium alkaloids have no effect on the hyperglycemia resulting from the conversion of hepatic glycogen (epinephrine or piqûre), but they have an inhibitory action on alimentary hyperglycemia (Klercker, 1914). This indicates that the action is on the alimentary canal, presumably by the gastric delay slowing the digestion and absorption of the carbohydrates, and thus preventing the sudden flooding of the organism with sugar (Macleod, 1914).

Relief of Diabetes.—Opium, morphine and codeine diminish the discomfort, the thirst, hunger and itching, and in moderate cases sometimes also the glycosuria, but not the hyperglycemia. The action would, therefore, appear to be on the renal threshold. The influence on the course of the disease is unfavorable and therapeutically inadvisable, even apart from the addiction danger (Chopra and Boxe, 1930).

Toxicology.—*Acute Symptoms of Morphine and Opium Poisoning.*—Suicidal and accidental poisonings by these agents are common. Prompt diagnosis is important for proper treatment. Coma is the most conspicuous symptom, and its gradual development is characteristic. In advanced poisoning it may be difficult to distinguish the morphine coma from other forms. The symmetrical pin-point pupils are important, but it must be remembered that these dilate as death approaches (asphyxia). The odor is distinctive for opium poisoning. The following description of the morphine effects applies equally to opium (with ten times the dose), except that the symptoms do not appear as promptly.

Moderate Therapeutic Doses (5 to 15 mg., $\frac{1}{12}$ to $\frac{1}{4}$ grain of morphine).—The symptoms set in five to ten minutes after hypodermic, fifteen to thirty minutes after oral administration. They begin with slight flushing of face, sensation of warmth and comfort, lassitude, giddiness, dreamy state, with free imagination but confused intelligence; mouth dry and thirsty. The patient then becomes sleepy; skin pale; respiration and pulse slowed; pupils constricted. Nausea and vomiting are exceptional with this dosage. In a short time—the sooner, the larger the dose—a natural sleep sets in, lasting six to eight hours or more; the patient commonly awakens refreshed. *Intravenous injection* may produce immediate tinnitus, tachycardia and brief fainting.

Larger Therapeutic Doses (20 to 30 mg., $\frac{1}{3}$ to $\frac{1}{2}$ grain).— The initial symptoms are the same. Sleep occurs more promptly and is more profound. On awakening there is usually some confusion, nausea, anorexia and constipation.

Toxic Doses (100 to 300 mg., $1\frac{1}{2}$ to 5 grains). —The initial symptoms are as described. The somnolence deepens rapidly into sleep and coma; severe symptoms are generally conspicuous in five to ten minutes after hypodermic, or fifteen to forty minutes after oral administration; rarely delayed for one or two hours. In the earlier stages of the coma the patient can be partially aroused to a confused consciousness, but relapses promptly into lethargy. As the coma deepens (*i. e.*, almost always within two hours, and often in half an hour after taking the poison), the patient can not be roused, the reflexes disappear, the muscles relax, the jaw drops. The miosis becomes extreme ("pin-point pupil"); the skin cyanotic; the temperature falls; respiration is very slow, irregular, often Cheyne-Stokes; pulse slow, feeble and often irregular. Convulsions are rare in adults, more common in infants; they are sometimes violent, but rarely if ever tetanic. The respiration stops before the heart. The pupils almost always dilate as the terminal asphyxia sets in. (With heroin, death is due to the convulsions; Langer, 1912.) The *time of death* is usually seven to twelve hours; but sometimes two hours or even less. Survival over twelve hours indicates a good prognosis. *Autopsy findings* are merely those of asphyxia: cerebral and meningeal congestion, sometimes with serous effusion; lungs hyperemic and sometimes edematous; general venous congestion; rarely intestinal or cerebral ecchymoses.

Recovery may occur even after asphyxial convulsions. The respiration and pulse improve, the coma becomes lighter and passes into a prolonged sleep, often lasting one or two days. On awakening, the patient is troubled with headache, constipation and digestive disturbances, often vomiting, itching, impotence of the bladder, exceptionally excessive depression. Sometimes the recovery is interrupted by a serious relapse, perhaps through the reabsorption of morphine from the intestine.

Ordinary Fatal Dose.—With morphine, this is 0.2 to 0.4 Gm. (3 to 6 grains); with opium, 3 Gm. (45 grains). There is considerable idiosyncrasy, and 60 mg. (1 grain) of morphine must be regarded as dangerous. With 250 mg. (4 grains) the prognosis is unfavorable, even under treatment, although patients have been saved after 4 Gm. (60 grains) of morphine.

A few cases of death from ordinary doses of opium have found their way into the literature, but their significance is doubtful; E. E. Smith in 1854 reported in the "Lancet" the death of a two-day-old infant from 5 mg. of opium; and cites from a Mr. Dendy that 8 mg. of opium had produced dangerous poisoning in a child of two years. Lewin (Gifte und Vergiftungen, p. 612) states that death of adults has been reported from 0.3, 0.5 and 0.6 Gm. of opium.

In *acute heroin poisoning*, the animals are killed by the convulsions; if these are prevented by etherization, almost double the fatal dose may be survived (Langer, 1912). The literature of fatal heroin poisoning is reviewed by McNally, 1917.

Relative Toxicity for Different Animals.—The tolerance for morphine differs remarkably. Comparisons of the toxicity of morphine and its derivatives (M. Osman, 1929) can, therefore, not be transferred from animals to man. Man is by far the most susceptible to morphine, the fatal dose for man being no greater than that required for a frog of but $\frac{1}{2000}$ the weight. Pigeons, goats, rabbits and pigs require nearly one hundred times the human dose, per kilogram; dogs and cats about fifteen times; horse and cow two to four times. The toxic levels for *hamsters* are given by D. B. Houchin, 1943.

Idiosyncrasies.—*Infants* are highly susceptible to morphine; there is difference of opinion as to older children. Women and patients weakened by disease succumb relatively easily. *Myxedema* lowers the tolerance, so that 15 mg. of morphine may put a patient into deep coma (Lund and Benedict, 1929). In *uremia* there may be synergistic coma with magnesium, if this is administered as cathartic (Hirschfelder). On the other hand, large doses are well tolerated in *diabetes, delirium tremens, tetanus, hydrophobia* (Cl. Bernard), and during the severe and persistent pain of *biliary or renal colic*. *In shock*, the poor absorption may delay and so diminish the response to hypodermic injections of morphine. If it is attempted to compensate for this by repeating the injection, the whole amount may be absorbed at once when conditions improve, and produce dangerous poisoning (H. K. Beecher, 1944). In *fever*, morphine is sometimes exciting; in neurotic patients it may cause insomnia and delirium instead of sleep. Nausea and vomiting are pronounced in some individuals. Persons with high parasympathetic excitability react even to small doses with severe and prolonged vomiting and fall of blood pressure, sometimes with collapse. Urticaria has been observed. *Itching of the skin*, especially of the nose, is a rather common symptom in poisoning. These idiosyncrasies should be remembered in the therapeutic use of the drug.

Hypersusceptibility of Infants.—Young animals are said to be more susceptible than adults, with the exception of cats. Doebeli, 1911, from a clinical and experimental investigation, concludes that the hypersensitiveness, both in the human and in animals, applies only to the age before weaning, older children following the ordinary rule. The hypersusceptibility exists only for the narcotic action and is, therefore, less significant for codeine. The experimental findings are confusing. Chesler *et al.*, 1942, report that fetal and adult rats are equally susceptible to acute respiratory failure, and that the newborn are more resistant. Gibbs and Bobb, 1938, found the toxicity of morphine for newborn rats ten times that of adults; it then decreases steadily to the twenty-first day, when it reaches the adult level. In rabbits, the susceptibility to the convulsant and fatal effects of morphine decreases to about the twelfth week of life, and increases from the twelfth to twenty-fourth week. Morphine derivatives do not give the same curve (Eddy, 1939). The special susceptibility of sucklings is perhaps explained by the observation of Hunt, 1910, that a *milk diet* greatly increases the toxicity of morphine (for mice). *Rachitic diet* renders cats less susceptible to the depressant and more susceptible to the stimulant action (Amsler, 1937), probably because calcium deficiency renders the central nervous system more excitable. Hunt, 1905 and 1907, found that *feeding with thyroid or iodides* increases the susceptibility of mice, rats and guinea pigs to morphine. Githens and Meltzer, 1913, find in rabbits that iodide increases the morphine depression but lessens the tetanic effect, and therefore the fatality. It has been claimed (Lewis and Scott) that *adrenalectomy* renders rats much more susceptible to the lethal effects of morphine, but Rogoff, 1925, showed that this was based on inadequate estimates of the natural mortality after this operation, and that the susceptibility to morphine is not altered. *Double nephrectomy* is said to increase tolerance for morphine (E. M. McKay and McKay, 1930)

Treatment of Acute Morphine and Opium Poisoning.—If the opiate was taken by mouth, the first indication is to *empty the stomach*. If narcosis has already set in, emetics may act too slowly and the stomach tube should be used. The best *chemic antidotes* are activated charcoal (a tablespoonful or more, stirred into water) or potassium permanganate, 0.5 Gm. per liter by lavage; or orally, 0.1 Gm. in a tumbler of water. Tannic acid is not very effective. The patient should be *kept awake* as far as possible, by talking, hot strong coffee and constant movement, to counteract the lethargy. Reflex stimulants may be employed, such as cold ablutions and the inhalation of ammonia in the form of smelling salts. The patient should be kept *warm*. Metrazol and nikethamide are generally considered the most effective respiratory stimulants in morphine poisoning (Schübel and Gehlen, 1928); Handley *et al.*, 1944, report amphetamine, 5 to 25 mg. hypodermically, more effective. If the breathing shows signs of failing, artificial respiration should be supplied. *Oxygen* inhalation is also useful in the later stages (periodic respiration and anoxemia); it increases the rate of respiration and improves the blood pressure (Clark and Hamill). When the danger is over, the *constipation* which usually follows should be relieved by cathartics and enemas.

Permanganate.—De Busscher (1904, 1905) found this effective in rabbits, even when it was administered three hours after the morphine; it was much less successful with dogs. It was quite ineffective if the morphine was given subcutaneously.

Respiratory Stimulants.—If the morphine asphyxia is interpreted as inattention to the CO_2 stimulus, a removal of this psychic fog would be required to restore permanently the excitability of the centers. No drug has yet been found quite successful for this purpose; the "improvement" is usually confined to an acute and temporary reaction. The discordant conclusions of a few workers may be quoted in illustration: *Voegtlin and Wiggers*, 1918: caffeine, moderate doses, marked improvement; atropine, slight improvement; camphor and epinephrine, doubtful. *Meissner*, 1923 (rabbits): improvement by ether or atropine hypodermically, camphor or cocaine intravenously. No improvement by caffeine, strychnine, epinephrine and aspidospermine. *Schmidt and Harer*, 1923 (dogs and cats): caffeine, marked increase of rate and depth of respiration; aided by digitalis; camphor, variable; atropine, ineffective; CO_2 inhalation, dangerous. *Haskell et al.*, 1924: caffeine, in wide range of doses, unfavorable. In *human subjects*, with respiration depressed by morphine, the increase of minute-volume averages 102 per cent for amphetamine, 37 for nikethamide, 30 for ephedrine, 21 for metrazol, 17 for caffeine (C. A. Handley, 1945).

A general antagonism exists also between morphine and small doses of *cocaine*, especially as regards the effects on temperature and metabolism. Larger doses are synergistic.

Atropine has been used extensively and somewhat indiscriminately in the treatment of morphine poisoning. It may be a dangerous remedy. The most conspicuous antagonisms of the two poisons are on functions of subordinate importance to life, on the pupils, heart rate and secretions. The more important effects on respiration, circulation and metabolism are antagonistic only with certain stages; while more severe grades are actually synergistic. The later paralytic effects of atropine coincide with those of morphine; while in the last stages of morphine poisoning the centers are too greatly depressed to respond to the slow and weak stimulation of atropine. *The usefulness of this antidote exists therefore only if moderate doses of atropine are given in moderate morphine poisoning* (or *vice versa*). This conclusion is supported by several series of experiments on animals. As a practical deduction, the atropine should be given hypodermically in the dose of 1.5 mg. ($\frac{1}{40}$ grain) and should *not* be repeated. It is fair to add that this is not the universal opinion. For instance, Roch, 1907, advises 2 mg., frequently repeated, until the pupils begin to dilate.

Comparison of Morphine Derivatives.—The complex chemical structure of morphine lends itself to innumerable modifications. Some of the more simple are represented in the opium alkaloids. More profound alterations have been produced artificially (including related synthetic derivatives of phenanthrene, carbazol and dibenzofuran), especially by L. F. Small and Mosettig, and investigated experimentally by Eddy and clinically by Himmelsbach and their collaborators, for the Narcotic Addiction Committee of the National Research Council, 1938 to 1941. Such investigations require objective methods and critical interpretation to guard against premature enthusiasm which has often characterized the commercial exploitation of morphine substitutes. The modern investigations have confirmed that unless the changes involve rather profound dislocation of the structure, the actions of the derivatives are qualitatively identical with those of morphine, but they differ in potency and in the relative effects on various organ systems, and these differences are of practical importance. Considerable is now known as to how these correlate with the chemical structure.

Muzzling the *phenolic OH* of morphine by alkyl or aryl groups almost invariably increases the convulsant action and sometimes the toxicity, and decreases all other morphine effects, regardless of what other modifications may be made elsewhere in the molecule. Covering the *alcoholic OH* tends to increase *all* the morphine actions, but generally to shorten their duration. Spatial shifts in the alcoholic OH have irregular effects Saturation of the C 7.8 double bond tends to increase the potency and duration of action (summary, C. K. Himmelsbach, 1941).

It is questionable whether any of the derivatives that have been investigated surpass morphine and codeine in therapeutic adaptability. The distinctive features of the more important agents may be recapitulated.

Morphine produces the strongest narcotic, analgetic, hypnotic and intestinal effects, and has the weakest convulsant action. It causes the greatest derangement of digestion, and, next to heroin, is most liable to induce addiction. It could cover all therapeutic indications. The chief objections are the addiction liability; and to a minor degree the nausea, constipation and occasional idiosyncrasy. If it is properly dosed and spaced it is probably more satisfactory for analgesia than its derivatives (E. L. Lee, 1942).

Opium produces essentially the effects of the morphine it contains (10 per cent), except that the gum and other extractives somewhat delay absorption, and render it unsuitable for injection. The modifications induced by its other constituents are slight and not especially important. This applies also to mixtures of opium alkaloids such as *pantopon* (J. H. Hayman and Fox, 1937; Barlow, 1937). The differences which are reported by various observers are so contradictory that they were probably accidental.

Pantopon (pantopium hydrochloricum), introduced by Sahli, consists of the isolated alkaloids of opium in their natural proportions. Its effects are essentially those of its morphine content. The earlier pharmacologic data on pantopon are reviewed by Barth, 1912. Severe poisoning from 50 mg. is reported by Voigt, 1911. *Artificial mixtures* of opium alkaloids have been proposed, such as the *laudanons* of Faust, 1912, and the *narcophine* of W. Straub and Caesar, 1912, with claims that they represented optimal potentiations of the phenanthrene and isoquinoline alkaloids; but the claims were not substantiated by other workers (Weissner, 1914). *Potentiation of Toxic Action:* Issekutz, 1912, found that the toxicity of mixtures of morphine and its esters corresponds to simple addition, but that mixtures of these with the isoquiniline alkaloids show marked potentiation. This has been confirmed by W. Straub and Caesar, 1912, who claim that doses of narcotine, which are in themselves inactive, double the toxicity of morphine for mice.

Codeine (methyl morphine) is less narcotic and especially less nauseant and constipative than morphine. It is much less likely to induce addiction (chiefly because it gives less abrupt elation, and is expensive and more difficult to inject in large dosage). It should be preferred whenever possible. It is adequate against cough, discomfort and moderate pain, not against severe pain or against diarrhea. Increase of dosage is liable to produce restlessness instead of quiet. Infants are not hypersusceptible (Doebeli, 1911).

Codeine was isolated by Robiquet in 1832, but did not come into general clinical use until 1880. In animals, codeine increases the spinal reflexes distinctly more than morphine (v. Schroeder, 1883), and it may be more toxic through the convulsions. Cl. Bernard reported that it never puts dogs as completely asleep as does morphine, but that the chief difference is in the awakening, which is not accompanied by the fright, hyenoid posture and dementia that characterize morphine recovery in dogs. Frankfurter and Hirschfeld, 1910, claim a greater dilation of the *cerebral vessels* (without rise of blood pressure).

Convulsant Narcotic Series.—In general, the narcotic actions on the brain, on the one hand, and the stimulant action on the cord and medulla, on the other, are in inverse ratio: morphine is the most narcotic and least convulsant, and thebaine the most convulsant and least narcotic, the other morphine esters and the isoquinoline alkaloids being intermediate. Buergi, 1914, places them as: morphine, papaverine, codeine, narcotine, narceine, thebaine. *Thebaine* (dimethyl-morphine) is so markedly convulsant that it may be placed in the strychnine group (Cl Bernard; Stockman and Dott, 1890).

Ethyl-morphine (*dionin*) is used chiefly for its local edemic effect on the conjunctiva. Its central actions are in all respects intermediate between those of morphine and codeine.

Diacetyl-morphine (*heroin*) stands closer to morphine, of which it shares all the disadvantages, without any serious advantages. It is more addictive. Its manufacture and importation are prohibited in the United States.

Dihydromorphinone (*dilaudid*), an artificial derivative, is more potent than morphine, producing equal narcosis with $\frac{1}{5}$ to $\frac{1}{4}$ of the dosage. It is perhaps less nauseant and constipating, but as it is fairly addictive (clinically, King, Himmelsbach and Sanders, 1935; experimentally, E. J. Stanton, 1936), its usefulness is questionable (review, N. B. Eddy, 1933). The dosage averages about a fifth that of morphine; for cough, 1.3 mg., $\frac{1}{40}$ grain; as analgetic, 2 to 2.5 mg., $\frac{1}{32}$ to $\frac{1}{24}$ grain. The action is somewhat less lasting.

Dilaudid was introduced clinically by Krehl, 1926, after a rather brief pharmacologic study. The superiority as to digestive disturbance (Gottlieb, 1926) may be questioned. King *et al.* found it clincially just as constipative as morphine; Krueger and Holmes, 1934, report vomiting in dogs and obtained the same effects as with morphine on Thiry-Vella fistulas in unanesthetized dogs. Like morphine, it is deliriant to cats (J. Schmitt, 1929) and excitant for horses, and somewhat for dogs (F. Oehme, 1928).

Methyl dihydromorphinone (*metopan*) is the most promising of the derivatives so far developed by Small and Mosettig. Its nauseant action is less, its toxicity greater, its analgesia somewhat more potent than with morphine and distinctly more persistent, and tolerance seems to be less readily acquired (N. B. Eddy, 1938). It satisfies the craving of morphine addicts and is, therefore, potentially addictant, but there is probably less danger since tolerance is not readily acquired, so that the dosage need not be increased. It is especially suited for controlling chronic pain, like that of cancer, with about half the dosage of morphine. It is less suitable as preanesthetic sedative, being less somnifacient, and sometimes produces respiratory depression (E. L. Lee, 1942). *Dihydrodesoxymorphine* (*desamorphine*), one of the derivatives devised by Small and Mosettig, appeared to have favorable therapeutic ratios, its toxicity (in animal experiments) being four times that of morphine, analgetic potency ten times, gastro-intestinal action, only $\frac{1}{20}$ (Small and Eddy, 1934). However, the action lasts only three-fourths as long as morphine, requiring frequent administration, and this increases the addiction liability. It is adequate for preanesthetic sedation, but its advantage is questionable (Lee, 1944). *Eukodal* was reported by Dixon as especially addictant and dangerous.

Synthetic phenanthrene derivatives acquire marked analgetic actions, especially by substitution of OH and NH_2 groups. Some derivatives synthesized by Mosettig cause a veratrine-like prolongation of relaxation in muscle (Small *et al.*, 1938). In Straub frog hearts, they disturb the ventricular rate without changing that of the auricles. The block is not modified by atropine (E. E. Nelson, 1939).

Other Constituents of Opium.—The isoquinoline alkaloids are discussed under Papaverine (see Index).

Meconic Acid has no effect in the doses which would be administered in opium. Larger doses produce narcosis, muscular fibrillation, medullary convulsions, diarrhea, curare action (Barth, 1912).

Regulations for the Prescribing of Narcotics.—In the United States, physicians who prescribe narcotics must be registered with the Department of Internal Revenue, and comply with regulations furnished by that department, which are designed to restrict the illegitimate supplies of these drugs. Severe penalties attach to violations.

Form of the Prescriptions.—These are written on ordinary blanks, *not* on special forms. They must contain: (*a*) The full name and address of the patient; (*b*) the full name, address and registry number of the prescriber, and (*c*) the date of issue. The signature must be in ink or indelible pencil. Narcotic prescriptions can not be given over the telephone. They can not be refilled or partly filled. A physician is permitted to prescribe only for patients whom he attends in person.

Prescriptions for continuous use must have further inscriptions explaining the facts or the "exception" under which they come; for incurable diseases they may be marked, "Exception I, Article 117"; if for addicts under the special restrictions provided in "Exception II, Article 117" (Treasury Decision 342).

Scope of the Regulations.—These include opium or coca leaves, or any compound, manufacture, salt or preparation thereof, even though they are not narcotic, for instance apomorphine and papaverine. Synthetic local anesthetics are not included.

Exemptions.—Certain articles are specifically exempted and may be prescribed without formality or bought without prescription, for legitimate uses. The more important of these exemptions are: Tr. Opii Camph.; Mist. Opii et Glycyrrh. Co.; Lotio Plumbi et Opii and all preparations for application on the skin, if they contain ingredients that would render them unfit for internal use.

Conditions against Which Narcotics May be Prescribed.—These include, (*a*) all acute conditions, at the discretion of the prescriber; (*b*) incurable diseases (cancer, advanced tuberculosis, etc.) under certain restrictions; (*c*) the treatment of addicts, narrowly restricted.

Dispensing and Administration of Narcotics by Physicians.—Subject to the preceding paragraph, physicians may personally administer single or occasional doses away from their office, without formality or record. Otherwise a record must be kept, in the manner provided in the regulations.

PREPARATIONS—OPIUM

***Opium,** U.S.P. (*Meconium,* Thebaicum), is the dried milky juice exuding from the incised unripe seed capsules of the poppy, Papaver somniferum. Brown masses or powder of peculiar odor and bitter taste. Contains a number of alkaloids, the most important being morphine (not less than 9.5 per cent). Prescribed as *Powdered Opium,* U.S.P. (Opium Pulveratum), a light brown powder, yielding 10 per cent of anhydrous morphine. Dose, 0.03 to 0.2 Gm. ½ to 3 grains. The usual percentage of the other alkaloids in opium is: Codeine, 0.2 to 0.7 per cent; Thebaine, 0.15 per cent; Narceine, 0.02 to 0.7 per cent; Narcotine, 1.3 to 10 per cent; Papaverine, 1 per cent (absent in some sorts; Van Italie and Kerbosch, 1910). The development of these alkaloids in the growth of the plant is interesting (Kerbosch, 1910). Opium also contains a number of other minor alkaloids: meconic acid (2.5 to 5.5 per cent), lactic acid, gums. resins, fats, odorous principles. No starch or tannin. The most important preparation is **Opium Tincture,** U.S.P. (*Laudanum*), 10 per cent of opium or 1 per cent of morphine. Miscible with water or alcohol. Dose, 0.6 cc., 10 minims. The ***Camphorated Opium Tincture,** U.S.P. (*Paregoric*), is a weak (0.4 per cent of opium) aromatized preparation, forming a milky mixture with water. It is used especially against diarrhea and for children. Dose, 2 to 4 cc., ½ to 1 drachm. Four cc. contain 16 mg., ¼ grain, of opium or 1.6 mg., 1/40 grain, of morphine, U.S.P. (20 mg., ⅓ grain, of opium or 2 mg., 1/30 grain, of morphine, B.P.). ***Compound Mixture of Opium and Glycyrrhiza,** U.S.P. (*Mistura Opii et Glycerrhizae Composita; Brown Mixture*), is used as sedative expectorant. Ten cc., 2½ drachms, of this mixture contain 1.2 cc. of paregoric or 5 mg., 1/12 grain of opium; and 2.5 mg., 1/24 grain of tartar emetic, also a little Sp. Aeth. Nitrit. It is needlessly complex, but the tartar emetic effectively prevents increase of dosage. Dose, 4 cc., 1 drachm, U.S.P.

Pantopon (*Pantopium Hydrochloricum*) is a purified mixture of opium alkaloids, containing 50 per cent of morphine. Sol. in water. Dose, 5 to 20 mg., 1/12 to ⅓ grain, by mouth or hypodermically.

Dover's Powder, U.S.P. (Pulvis Ipecacuanhae et Opii), containing 10 per cent each of ipecac and opium, has only historical interest. It was introduced by Thomas Dover, 1742, as a diaphoretic in gout. Dose, 5 to 10 grains.

PREPARATIONS—MORPHINE

***Morphine Sulfate,** U.S.P. (Morphinae Sulfas), *Morphine Hydrochloride,* B.P., and other morphine salts occur as odorless, bitter, white feathery crystals. They are incompatible with alkalis, tannin, iodides and other precipitants of alkaloids. The sulfate is soluble in 16 parts of water (the hydrochloride in 17.5; free alkaloid in 3340 parts). The B.P. lists a 1 per cent Liquor Morphinum Hydrochloride. Average dose, 10 mg., ⅙ grain. The rectal dose is the same; the hypodermic about two-thirds of the oral. Maximal single dose, 30 mg., ½ grain. The usual dosage for special indications is: 2 to 5 mg. for cough and diarrhea; 5 to 15 mg. for pain and insomnia; 10 mg. for preanesthetic and in hemorrhage; 15 mg. in dyspnea, colic, peritonitis. Solutions are said to decompose rather readily when heated above 60° C. (Welmans, 1908). Moulds in solutions of morphine often come from the cork. They are prevented by adding a small piece of camphor (Norgaard, 1920). *Morphine Sulfate Tablets,* U.S.P.; the usual sizes contain 5, 8, 10, 15 and 30 mg. (1/12, ⅛, ⅙, ¼ and ½ grain). *Morphine Injection,* U.S.P., a morphine salt in water for injection; usual sizes 10, 15, 20 and 30 mg. (⅙, ¼, ⅓ and ½ grain) in 1 cc.

The *dosage of opiates for children* is best adjusted to the weight: with children above ten months, the weight (in pounds) is divided by 150; below ten months, by 300. The adult dose is multiplied by the fractions thus obtained (Doebeli, 1912). H. E. Irish, 1935, concludes that the effects on infants are simply proportional to the body weight.

PREPARATIONS—MORPHINE DERIVATIVES

These resemble morphine salts in physical characteristics and incompatibilities.

***Codeine Sulfate,** U.S.P., is soluble in 30 parts of water (*Codeine Phosphate,* soluble in 2.5 parts, is also official in the U.S.P.). Dose, (15 to 60 mg. ¼ to 1 grain). *Codeine Phosphate Tablets,* U.S.P., and *Codeine Sulfate Tablets,* U.S.P.; the usual sizes contain 15, 30 and 60 mg. (¼, ½ and 1 grain).

Dihydromorphinone Hydrochloride, U.S.P. (*Dilaudid*), N.N.R., differs from morphine by the substitution of a ketone group for one of the hydroxyls and the removal of the adjacent double bond by hydrogenation. Soluble in water (1 Gm. in 3 cc.). Marketed as tablets of 2.5 mg.; hypodermic tablets of 1, 2, 3.2 and 4 mg., and ampuls of 2 mg. in 1 cc. Dose, as sedative and analgesic, 2.5 mg. orally or 2 mg. hypodermically. In mild pain or cough, 1.3 mg. by mouth. *Dihydromorphinone Hydrochloride Tablets,* U.S.P.; the usual sizes contain 1, 2 and 4 mg

Ethylmorphine Hydrochloride, U.S.P. (*Dionin*), is soluble in 10 parts of water. Dose, 15 mg., ¼ grain; locally, 10 to 20 per cent. *Diamorphine Hydrochloride,* B.P. (*Heroin,* Diacetyl morphine), is soluble is 2 parts of water; dose, 2.5 to 8 mg , 1/24 to ⅛ grain.

OPIATE ADDICTION

Opium, morphine and its derivatives, especially heroin, and to a less extent cannabis and cocaine, may lead to serious addiction, based on the euphoria which they produce, the feeling of well-being, relief and contentment, of stimulation and freedom of imagination, and of ease and facilitation of mental effort. These grateful actions vary in kind and degree for different individuals, as also the will and the ability to resist the temptation, and therefore all do not fall victim to them with equal readiness; adolescents, women, emotionally unstable, neurotic and dissipated individuals are especially in danger if they become acquainted with the effects of these drugs. The greatest number begin their addiction at the age of 20 to 29 years; next come the adolescents; few start after fifty (Pescor, 1938). Drug addiction is generally a symptom of psychologic maladjustment, "an attempt to escape the unhappiness of a losing battle with life." The elation itself is largely the relaxation afforded by relief from an incubus and is therefore proportional to the burden or boredom. The majority of the heroin and cocaine addicts belong to the criminal classes, thrill-seekers and hedonists, who begin the use through curiosity or dissipation (Kolb and Ossenfort, 1938; Treadway, 1930; J. R. Rees, 1932; Felix, 1939); next comes the medicinal use, especially against pain (U. S. Treasury Report, 1931); and next perhaps those who are tempted to occasional use in times of stress and fatigue. The expense and the difficulty of obtaining the drugs have largely eliminated the casual users. Before the restriction of the Harrison Narcotic Law, "patent medicines," cough, consumption, diarrhea, and catarrh "cures," were responsible for many cases. Infants have become addicted through paregoric and "soothing syrup." Addiction in pregnancy produces addiction phenomena, tolerance and withdrawal symptoms in the newborn, in animals as well as in the human (K. Rai, 1937). Physicians must be on their guard when prescribing these drugs in acute conditions. Their frequent use for minor discomforts leads easily into temptation. The continued administration is justifiable only in hopeless painful diseases, such as cancer. They are detrimental rather than helpful to the cure of tuberculosis. It is safest to assume that daily use will soon lead to addiction—ten days may suffice in susceptible individuals, and twenty to twenty-five days in those with normal emotional stability (Hubbard, 1920). All morphine derivatives may do so, including codeine, although this is unusual in practice. The liability is greater with the drugs and methods that give the promptest euphoristic "kick." It is therefore greater with intravenous than with hypodermic injection, and with this more than with oral use; with heroin more than with morphine, and with this more than with codeine. Frequent repetition is more habituating than larger doses farther apart. Increase of dosage is especially dangerous.

Prevalence of Opium Addiction.—While the therapeutic use of opium goes back beyond Hippocrates, its habitual use seems to be of more recent origin and was at first confined to the Orient. The first authentic records fall in the beginning of the sixteenth century. The Mohammedans learned it through the conquest of India. Their acquaintance with Cannabis indica was much earlier. Its introduction into Europe and America is of modern date. In the United States it was rare until after 1860. It increased greatly until it was checked by the Harrison antinarcotic act of 1915, which makes addiction illegal, inconvenient and expensive. The average addict now uses less than a grain of morphine per day (Anslinger, 1940). Further improvement in the narcotic situation depends on the success of police in dealing with smugglers and illegitimate dealers; on a popular understanding of the seriousness of starting the addiction; and on methods of treating confirmed addicts.

Accurate appraisal of the *number of opiate addicts* is not possible. Official estimates place the proportion in 1877 as 1:400 of the general population in the United States; in 1922 as 1:1000; in 1938 as 1:3000 (Anslinger, 1940), but it may not be more than 1:10,000, which is about the same as in Germany. The proportion is highest in the urban centers, and among young people. Nearly half the addictions start before twenty-four years of age (W. L. Treadway, 1930). Physicians have a considerably higher ratio; estimates run as high as 1 per cent (Anslinger; for Germany, Kurt Polish, 1931).

By far the largest proportion of drug habitués start as abnormal personalities who become addicted by choice, through associates or curiosity. Of about a thousand patients at the Lexington Narcotic Hospital, over half had a hedonistic personality, another fifth had inebriate histories, nearly a fifth were frankly psychoneurotic and psychopathic, and less than 4 per cent could be classed as normal (Pescor, 1939).

The legal consumption of opiates in the United States shows a distinctly favorable trend. Between the years of 1931 and 1935, the per capita annual consumption of the more addictant alkaloids decreased 20 per cent (from 2.8 to 2.3 grains, expressed as opium), while that of the less addictant codeine and dionin increased 2.3 per cent (from 2.85 to 3.5 grains, as opium). *Cocaine* decreased 13 per cent (from 6.84 to 6.06 grains) (U. S. Treasury Report, 1935). The total legal consumption in the United States in 1931 was (in ounces), codeine, 164,000; morphine, 90,000; cocaine, 32,000 (U. S. Treasury Report, 1931).

Forms of Opium Habit.—The drugs are introduced by all possible channels: by the mouth, hypodermically, intravenously, by smoking, by suppositories; and heroin, like cocaine, by snuffing. The effects are essentially similar. Addicts in the United States chiefly use heroin by snuffing, and this and morphine hypodermically or intravenously (since 1920), probably because of the more abrupt and therefore more noticeable response. Those who have become accustomed to injections do not readily change to the oral use. The needle may be attached to a medicine dropper; sometimes the alkaloids are rubbed in the scarified skin. The satisfaction of addiction involves something more positive than the mere suppression of physical discomfort. A "stabilized" dosage, which suffices to protect completely against active withdrawal symptoms, does not achieve the emotional tranquilization and "lift" for which the patient strives, and leaves a feeling of dissatisfaction (Himmelsbach *et al.*, 1940).

Smoking.—Smoking opium (chandoe) is prepared by the Chinese by a complicated process of roasting and repeated extraction and evaporation. Its morphine content is about the same as that of ordinary opium. Pott, 1912, and Nakajima and Kubota, 1927, proved that morphine is indeed the active constituent of the smoke. It has been said that Orientals are less injured by opium; but this is mainly because smaller quantities are consumed in smoking with longer intermissions. The hypodermic method has now become more popular, and with it the Chinese present the same phenomena as Europeans (A. S. Rochester, 1909). The Chinese government made serious and fairly successful efforts to suppress the opium evil. In *India*, where the use of opium was very prevalent but is rapidly diminishing, the dose is generally kept small, three to five grains of opium per day by mouth, which does not produce marked addiction phenomena. Those who take larger doses become addicted like Europeans (R. N. Chopra, 1928).

Addiction by Heroin.—All morphine esters may be presumed capable of producing addiction, but practically the difference between them is large. Heroin is more powerful than morphine, and the addiction is consequently more easily acquired and more difficult to break. It also causes more acute fatalities. Although its sale is prohibited in the United States, a considerable amount is smuggled, and the Atlantic seaboard addicts use it more than morphine (Treadway, 1930). The League of Nations Expert Committee (J.A.M.A.; *97:* 273, 1931) agrees that the objections to heroin are greater than its field of usefulness.

Addiction to codeine is relatively rare and generally easily broken; or else the patients go over to the other more effective and cheaper alkaloids (L. F. Davenport, 1938). Really narcotic doses would be inconvenient to administer, and disproportionately expensive, so long as its sale is restricted. If restrictions were removed so that it could be procured in unlimited quantities, the situation would become different. Large quantities were smuggled from Canada when its sale there was unrestricted (Commissioner of Narcotics, Report, 1936).

With medicinal doses of codeine, the psychic effects are so slight that they would scarcely be recognized by the patient; there is therefore little temptation to increase the dosage; and the codeine can be withdrawn without notable reaction. Relatively large doses over long periods appear necessary to establish addiction. Experienced addicts do not easily take to codeine, for while it removes the discomfort of the acute withdrawal symptoms (with about 5.2 times the dosage of morphine), it "leaves them cold," they do not achieve the euphoria, do not receive the "kick," even when the dosage is raised so as to produce narcotic confusion (Himmelsbach, Andrews *et al.*, 1940). Practically no fatalities from codeine are on record, and the fatal dose is not known. Small doses may cause symptoms if there is idiosyncrasy. *Derivatives of codeine* with more marked narcotic action produce addiction ("*eukodal*" and "*parakodin*"; Biberfeld, 1920 and 1921; P. Wolff, 1928). The acquired tolerance does not extend to the convulsant action.

Of fifteen *morphine derivatives* tested, all proved effective in satisfying the craving and other symptoms of morphine withdrawal in addicted patients and therefore possess addiction liability. Complete satisfaction occurred with dihydromophine, desomorphine and desocodeine; incomplete with metopon. Changes in the chemical structure alter the addiction liability in the same direction as other morphine actions, but perhaps not to the same degree. Clinically (Himmelsbach, 1941) as well as in animals (Small, Eddy *et al.*, 1938), methylation of the phenolic OH reduces the potency and prolongs the action. Replacement of the alcoholic OH by H or O increases the potency and shortens the action. Saturation of the C 7-8 double bond tends to increase both potency and duration. Isoquinoline derivatives, including perparine, are not addicting (Himmelsbach, 1939).

Effects of Opiate Addiction.—Continued use of opiates leads to the development of tolerance, to diminished response to its narcotic actions or, perhaps more correctly, to functional adaptation to the "fog," so that progressively larger doses must be used to secure the narcotic effects. Along with this, a craving for these effects develops, constituting the addiction; and if this craving is not satisfied, withdrawal symptoms set in, largely psychical but partly physical, which increase for several days, and then decline, so that the subject returns to a quasi-normal condition. Qualitatively, this is much like the course of other habitual indulgences, such as alcohol, tobacco, coffee or chewing gum; but the craving is so much stronger and the withdrawal reactions are so much more violent, that it is generally believed that a "physical dependence" is created. This is probably true, although it is difficult to prove and the concept is not very clear. However, animals (even completely decorticated dogs, A. Wikler, 1946) also develop the phenomena of opiate addiction, including tolerance, craving and withdrawal symptoms. The differentiation of "addiction" from "habit," and this from "habitual use" of a drug, is not sharply defined. Addiction and habit both involve an active desire, a hunger for the drug if it is withdrawn; they are generally held to differ in the degree of the acute ill effects of withdrawal, which are more serious with addiction. This distinction is of course arbitrary. "Tolerance" is not an essential part of addictions or habits, although it is frequently the case that experience dulls the reaction so that progressively larger doses must be used to produce equivalent effects.

Habituation of cold-blooded animals has not been adequately studied. Frogs are said to become hypersusceptible with repeated administration. An interesting reaction has been described for gold fish (not minnows): when placed in a "graduated tank," they rapidly develop preference for water containing alcohol, morphine and certain other substances (Shefford, 1918). However, this is probably a sensory skin phenomenon, and not analogous to the psychic craving of human drug habits

Acquired Tolerance.—The continued use of morphine or its derivatives leads to the gradual development of considerable tolerance to the narcotic and toxic effects. This starts before addiction becomes confirmed. Addicts who desire euphoria are therefore driven to the use of ever-increasing doses, sometimes 10 or 20 times more than would be fatal to an unaccustomed individual. The tolerance is never absolute, and accidental or intentional overdosage is a frequent cause of death for morphinists. Patients who take morphine as a stimulant may not increase their dosage beyond a definite, more moderate amount, soon ascertained by experience, and find it possible to resist or discontinue temporary increases beyond this point (Bishop); precisely as some smokers keep themselves on a fairly definite allowance while others are constantly increasing their indulgence. The daily consumption of morphine or heroin ranges between 0.3 and 4 Gm.; it is generally above 0.4 Gm. and would usually be between 1 and 2 Gm., if supplies were obtainable (McIver and Price, 1916; Kolb and DuMez, 1924; Wholey, 1912, heroin). Even larger doses are claimed by patients; but their statements are often unreliable, since they are made in the hope that the drug will be withdrawn more gradually. The tolerance diminishes if the drug is discontinued, but can be reacquired within ten days (Biberfeld, 1917). Some degree of tolerance persists indefinitely, so that the normal doses of morphine depress the pain threshold much less than with normal individuals (H. L. Andrews, 1943).

Mechanism of the Tolerance.—With the possible exception of rabbits (Van Dongen, 1915), all mammals and birds that have been tried acquire tolerance readily (Cloetta, 1903), and these have extended the possibilities of experimentation (review, Tatum and Seevers, 1931). The tolerance does not extend to all the actions, but only to those that involve conscious or subconscious psychic activity, including the respiratory center, which indeed acquires the highest tolerance (in dogs, 1800 times the initial minimal effective dose). Next comes the tolerance to narcosis, and then in descending order, defecation, emesis, and pupils (van Egmond, 1911). Cats also acquire some tolerance to the deliriant action (H. Gold, 1929). No tolerance is acquired by the cardiac vagus center, by the convulsive centers (Langer, 1912), or by the peripheral actions, the skin reaction (Pilcher and Sollmann, 1914) or the intestinal tonus and constipation (G. H. Miller and Plant, 1928). The undiminished response of the unconscious functions indicates that the tolerance of the conscious centers is functional, and not due to destruction or "antitoxic" inactivation of the alkaloid. The habituation may be interpreted as an education of the conscious centers to discount the morphine fog; possibly reinforced by the central hyperirritability which is an after-effect of morphine, conspicuous in the withdrawal symptoms.

The theory of hyperirritability was advocated by Tatum and Seevers, 1930, on the basis that monkeys with abstinence symptoms are hypersusceptible to cocaine excitement; and that animals habituated to morphine are tolerant not only to morphine derivatives, but also to depressants of other groups, such as barbital. The latter, however, is apparently not beyond the limit of error, for discordant results have been reported by other workers, also with chloral and scopolamine (Plant and Pierce, 1928). In any case, it would not be strange that adaptation to the morphine fog could be applied to barbiturate fog. On the other hand, habituation of cats to the deliriant action of morphine could not be explained by hyperirritability; nor the cross tolerance and emetic action of morphine and apomorphine, described by Tui, 1931; nor the fact that some degree of tolerance may persist for a considerable time. Indeed, C. F. Schmidt and Livingston, 1933, found that a single large dose of morphine renders dogs resistant to the narcotic effects of subsequent small doses. An erroneous hyperexcitability theory had been proposed by Marmé in 1883. He believed that morphine is transformed in the body into *oxydimorphine* (dehydromorphine), to which he attributed actions precisely the reverse of those of morphine. It would thus explain both the tolerance and the abstinence symptoms. Donnath, however, 1886, Marquis, 1896, and Schmidt and Livingston, 1933, showed that oxydimorphine is not formed; and, moreover, the properties of this substance do not agree with the assumption of Marmé. Another theory which may be dismissed is the formation of an *antitoxin.* Hirschlaff, 1902, claimed that the serum of habituated animals is protective; but his experiments are discredited by the negative results of Morgenroth, 1903, of Cloetta, 1903, and of Pellini and Greenfield, 1920, 1924. The blood of habituated animals (or man) contains neither protective nor toxic substances. *Increased destruction* of the alkaloids by habituated animals was reported by several workers, first for morphine by Faust, then for heroin by Langer, but later investigators found the destruction rate the same as for nonhabituated animals (Hatcher and Gold, 1929; Plant and Pierce, 1933), so that the apparent differences may lie within the experimental error. In any case, the destruction is so much slower than the absorption of the alkaloids (Cloetta, 1903; Ruebsamen, 1908) that it could not play an important role in the tolerance.

Psychic Effects of Opiate Addiction.—The immediate effects of morphine are essentially the same as in unhabituated individuals; but the response varies quantitatively, and somewhat qualitatively, because of acquired tolerance and of the imminence of "abstinence symptoms." These differ as regards the occasional opiate debauchee, and the steady addict. The *occasional user*, for instance the opium smoker, usually pushes the dosage to the toxic point, and thus obtains the dreams and the deep sleep. The steady consumer does not carry the dosage to that stage; partly because he has acquired tolerance; partly because of the side effects; and partly because it would be impossible for him to work while under the toxic influence. Most patients whose addiction started with the therapeutic use of opiates have never experienced the imaginative toxic effects, but only the analgesia and euphoria; their first recognition of the addiction dates often from the withdrawal symptoms. *Confirmed addicts* generally use opiates rather as stimulants, or as a means of escape from the intense discomfort, nervousness, depression and violent craving that follow the withholding of the accustomed dosage. These are analogous to intense hunger or thirst, and increase in intensity for several days to a degree beyond the unassisted strength of most patients, especially when the means of relief, further dosage of the opiates, is available to them (E. L. Bishop, 1913, 1920).

Apart from the dependence on the daily allowance of opiate, the imminence of craving and withdrawal symptoms when this is withheld, and the fear of detection, the condition of the addicted individual is quite normal even after long addiction to large doses (A. B. Light and associates, 1930) except for some tendency to constipation and alternations of moods of irritability and placidity or apathy, and corresponding changes in the pupils, coincident with the intervals of administration. The skin shows needle marks, and perhaps abscesses, if the drugs were injected. Intravenous injection with a common syringe has transferred *malaria* (Faust, 1933) and syphilis. A hundred fatal malarial infections from this source were reported in New York within four years. *Definite diagnosis* rests on failure to respond to therapeutic doses (15 mg., $\frac{1}{4}$ grain), and on the occurrence of withdrawal symptoms when access to the drug is prevented. It is also feasible to demonstrate morphine in the urine.

If the patient has difficulty in obtaining the drug, the picture is dominated by the withdrawal symptoms and their dread, and often by the consequences of the economic distress, especially in old cases which require large quantities of the drug. Such patients are emaciated and anemic, from starvation and bad hygiene. The skin appears cachectic, waxy pale, dry and rough; the nails and teeth are also often diseased from neglect. If the food is not restricted, the patients may be well nourished. The *basal metabolism* may have rather wide fluctuations, presumably because of the alternation of irritability and apathy. The abnormal life of extreme addiction is likely to accentuate the *neurotic tendency* which is usually inherent in these individuals. The *sexual functions* are often diminished (amenorrhea, functional impotence), chiefly by malnutrition, but libido is not completely abolished until the daily dosage of morphine reaches 1 to 2 Gm., 15 to 30 grains (Pescor, 1938); they generally return after withdrawal (Wholey, 1912). The estrous cycle and fertility of rats are not affected by morphine or cocaine addiction (H. B. Myers and Flynn, 1928; A. Forster, 1928).

Opiate debaucheries doubtless accentuate the weaknesses of *moral character* from which they originate. They tend to make their victims slothful, apathetic and unreliable. They do not lead to the more active crimes, as cocaine may, except in so far as crime may be necessary for obtaining the drug. (The relations of narcotic addiction and crime are reviewed by P. O. Wolff, 1943.) Those of inherently good character, if they take the drug solely to ward off the intolerable depression, are not so seriously affected. Their will power and self reliance are weakened, as by any other enslaving self indulgence, and the agony of drug deprivation drives them to deception and more serious crimes when their supply is threatened; but aside from this, their character and mental faculties remain practically unchanged. This is certainly the case in the legitimate continued use of opiates, as in cancer. A large part of the traditional depravity of the addicts exists in the minds of the public more than in life. This pariah attitude makes it more difficult for the addicts to lead a normal existence, and thus tends to drive them into the vices of which they are accused (Bishop). Drug addicts are patients with a nervous disease. Like other mentally ill patients, they must be treated with firmness, but also with sympathy and kindness.

The phenomena, as studied in *planned re-addiction* of former habitués, include *increase* of body water, erythrocyte sedimentation rate, carbohydrate intake, and of nocturnal activity; and *decrease* of body weight, pulse rate, basal metabolic rate and diastolic blood pressure. Respiration generally remains subnormal during addiction. *Efficiency,* as judged by psychologic tests, is lowered by slowing of responses, although not sufficiently to disrupt working efficiency seriously. Psychical stimuli produce less disturbance. Slight withdrawal symptoms begin within three weeks unless the dosage is progressively increased (E. C. Williams and Oberst, 1946; R. H. Brown, 1946).

Brain Potentials.—These show a high alpha index during addiction, persisting during and sometimes after withdrawal. Delta activity is present in severely addicted subjects, and is greatly reduced after withdrawal (H. L. Andrews, 1941).

Differential Action on Sensations.—In individuals not accustomed to morphine, this diminishes pressure and pain sensations about equally. Heat and cold appreciation are not impaired. The potency against pain declines with habituation, but that against pressure is not decreased. The analgetic potency returns on withdrawal. The discrepancy between the appreciation of pain and pressure therefore reflects the degree of active opiate addiction (P. Hoefer, 1929).

Suggestibility.—When tested by the "postural sway" suggestion, individuals addicted to opiates are distinctly more suggestible; this fades to normal on withdrawal (V. H. Vogel, 1937).

Hyperglycemic Tendency.—The blood sugar level is normal (except early in addiction, when it is high; Asho-Ro, 1934; H. Jacoby, 1930), but dextrose administration produces marked alimentary hyperglycemia in addicted individuals, both human and dog, levulose only in the human and not in the dog. Both tolerate high doses of insulin without hypoglycemia. It is suggested that this is related to liver pathology (Anton and Birk, 1934). On the other hand, the hyperglycemia reaction which follows the injection of morphine in normal dogs disappears after repeated injections, in two to four days (Pierce and Plant, 1928).

Water Balance.—In a series of addicts with marked physical dependence, the blood was found hydrated during addiction, less hydrated during withdrawal, returned to the addiction level after recovery from the withdrawal symptoms and later remained at the normal level (E. G. Williams, 1939). It is practically normal in moderate addiction, including the blood count (and blood picture) (Morat, 1911, human; Pierce and Plant, 1928, dogs). Barbour *et al.,* 1929, report slight hydration of the blood in dogs. They also found distinct hydration of the blood and tissues early in the addiction of rats by large doses of morphine, but this tended to return to normal as the addiction progressed. Rats addicted to morphine for six weeks develop moderate tissue edema, especially in the skin. This tends to disappear on the first day of withdrawal, but to recur during the second and third day. Parathyroid injections together with high calcium diet increase the water loss on withdrawal, tend to prevent the relapse, and diminish the withdrawal symptoms (Detrick and Thienes, 1941).

Metabolism in Animals.—Rats subjected to chronic morphinism, or to heroin or codeine, may be better nourished than the controls, probably because they are less active (Sollmann, 1924). They behave somewhat like thyroidectomized animals, showing a decrease of gas metabolism, increased respiratory quotient and increased sensitivity to oxygen deprivation (F. Hildebrandt, 1922). Excessively prolonged administration of morphine produces increased metabolism and progressive emaciation (Hildebrandt, Sollmann). The basal metabolic rate of addicted dogs is increased by about 10 per cent (Barbour *et al.,* 1939).

Effectiveness of Cocaine Anesthesia.—It has been claimed that the susceptibility of the cornea to local anesthesia is abolished during morphine addiction in humans and animals (Amsler, 1933), and that it is restored on dis-habituation, and also by milk injection even when the morphine is continued (rabbits, Bertschik, 1934). Others have failed to confirm the insusceptibility (Oelkers, 1935), and it did not exist in a man under active morphine addiction (Himmelsbach).

Withdrawal Symptoms.—The withdrawal of opiates from those habituated to their use is followed by craving and a train of severe nervous symptoms; the intensity varies with the individual, increasing with the stabilizing dosage (H. L. Andrews and Himmelsbach, 1944), the duration of the addiction, the dosage used, the rapidity with which the drug is withdrawn and being inverse to the general resistance, vigor and will power of the patient, much as with other ingrained habits. (The Philadelphia Committee, Light *et al.*, 1930, and King, Himmelsbach and Saunders, 1935, report comprehensive clinical studies.) In the early stages of addiction, withdrawal results in more or less restlessness, weakness and depression. These are endurable, and disappear in a few days if the drug is withheld. With more confirmed addiction, the symptoms take in general the following course: *Irritable temper*, uneasiness; *spasmodic yawning* and *sneezing*, lacrimation, coryza and hoarseness; *restlessness* and *weakness;* sweating, hot flashes and chills; leukocytosis (generally in the human; pronounced in dogs, Pierce and Plant, 1928); *severe functional digestive disturbances*, refusal of food and drink; vomiting and diarrhea, *concentration of the blood* and negative water balance, resulting in *loss of body weight* and shrunken skin; "*cramps*," muscular twitchings and violent pain in the legs, sometimes in the arms and abdomen; *headache* and other neuralgias; complaints of extreme *weakness*, tremors; *persistent insomnia*, excessive irritability, often culminating in hysteric attacks in women or in *delirium* and acute mania, sometimes suicidal; marked pilomotor activity. The most dangerous phenomenon is sudden circulatory *collapse*, starting with irregular and weak pulse, alternately fast and slow, cold sweat, general prostration, rarely ending fatally with heart failure. This collapse, if severe, demands the prompt injection of 10 mg. ($\frac{1}{6}$ grain) of morphine, which generally relieves all symptoms completely within five to thirty minutes; except that the concentration of the blood, and the cramps which probably depend upon it, may last for several hours until the water balance is restored.

With the abrupt and complete withdrawal, the symptoms are generally moderate on the first day, severe on the second and third, moderate on the fourth and fifth, mild on the sixth and seventh and absent on the eighth day. After ten to fourteen days, the patient generally begins to gain weight and appears well, although insomnia may persist for some time.

This grading is by the classification of Himmelsbach, 1936, as follows: *Mild grades* are characterized by yawning, lacrimation, rhinorrhea, sweating; *moderate grades* by gooseflesh, mydriasis, anorexia, tremor; *marked grades* by insomnia, restlessness, air hunger, rise of blood pressure (11 to 15 mm.), rise of basal metabolic rate, hyperglycemia, slight hyperpyrexia (0.5° C.); *severe grades* by exaggeration of the preceding, emesis, diarrhea and weight loss exceeding five pounds in twenty-four hours. Collapse is rare.

The withdrawal symptoms are largely, perhaps entirely, psychical, of the same nature as hunger, thirst or other intense craving, *i. e.*, quasi-hysterical reactions to a balked, imperative desire, more or less beyond volition. Those who have had much experience with treating addictions generally believe that there is also a "physical" dependence characterized by the physical withdrawal symptoms, which differentiates opiate from other addictions. The symptoms are stronger, however, if the patient expects, perhaps unconsciously, to arouse sympathy, and thus obtain the relief of the drug; they are practically absent if the patient is rendered delirious by scopolamine (Wagner and Riewel, 1905). Animals also react more or less to withdrawal (Plant and Pierce, 1928), with individual differences (Collins and Tatum, 1925; Sollmann, 1924), probably as they would to hunger and thirst

Intestinal Disturbances.—Roentgenologic examinations by Nishigiski, 1926, showed increased tone and peristalsis of the small intestines, or irregular progress of the contents, and spasticity of the large intestines; they are relieved by morphine, but atropine has little effect. Similar diarrheic withdrawal phenomena were observed by G. H. Miller and Plant, 1926, on dogs with permanent intestinal fistula. *Anorexia* is probably due to the malaise. In marked grades it decreases the caloric intake by 40 to 55 per cent.

The basal metabolic rate is increased in clinical withdrawal 21 to 30 per cent in marked grades (Himmelsbach), perhaps chiefly by the nervous unrest. It may exexplain the slight *hyperpyrexia*. In animals, Barbour *et al.*, 1930 and 1935, found the basal metabolic rate increased during withdrawal. Sudden withdrawal of morphine causes a marked temporary *rise of blood sugar* by 41 to 55 mg. per cent in marked clinical grades (Himmelsbach; Philadelphia Committee). It occurs also in rabbits (Asho-Ro, 1934) and dogs (Cohen). Clinically, the withdrawal illness is uniformly accompanied by *dehydration*, due chiefly to refusal to drink, together with the profuse sweating and diarrhea. It is partly responsible for the *loss of weight* (E. G. Williams, 1939); anorexia and increased metabolic rate are the other factors. Dehydration may also be a cause of the *muscle cramps*. These are not due to lowering of plasma calcium (E. G. Gross and Slaughter) In animals, morphine withdrawal may lead to increased water content of the blood (10 per cent) and of the brain (14 per cent), liver, muscle and skin (J. M. Pierce and Plant, 1928; Barbour *et al.*, 1928 and 1929). This is more marked on a carbohydrate than on a fat diet. Purging results in blood concentration (Morat, 1911). Thienes and Detrick, 1939, report that the tissue hydration of rats falls below normal during withdrawal. *Leukocytes* change in three phases: (1) a relative and usually absolute increase of neutrophils, generally with absolute lymphopenia and hypoeosinophilia; (2) near the middle or end of the first week, repeated fluctuations of the neutrophils and lymphocytes, and reciprocal, sometimes considerable eosinophilia; (3) restoration to the normal, sometimes requiring sixty days (M. Rinkel, 1933).

Nervous Withdrawal Symptoms in Animals.—Dogs, and especially monkeys, that have been addicted to opiates manifest satisfaction when these are injected, and abstinence symptoms when they are withdrawn, quite similar to the human. *Chimpanzees* resemble the human very closely. The addicted animals become introversive, less sociable, less playful, more cyclical in moods, restless when the time of injection approaches. Within two and a half to seven weeks of addiction they show definite withdrawal signs; yawning and a combination of restlessness and lethargy when the injection is deferred. They reach their maximum in forty-eight hours. Tolerance is also lost rather rapidly after this time and changes to hypersusceptibility. An important difference from human addiction is that the one animal studied two weeks after complete withdrawal apparently lost all interest in opiates, which it had sought strenuously during the active withdrawal symptoms. The time required to establish addiction was materially shorter when the dosage was increased (Spragg, 1940). *Macaca monkeys* are also well suited for showing addiction liability. Seevers, 1934, found the central depression more prolonged with morphine and dilaudid than with codeine and heroin. Tolerance developed most with morphine, then dilaudid, then heroin, then codeine. Withdrawal symptoms were least with codeine. *Completely decorticated dogs* may be addicted, much like normal dogs, becoming more resistant to the analgesia and sedation. They react to withdrawal by motor restlessness, rise of temperature, increased heart rate and rhinorrhea. These subside after three days (A. Wikler, 1946). *White rats* develop tolerance. They show no signs of satisfaction; but their struggle-response to the discomfort of restraint (tying to a board, in supine position) is greatly increased by withdrawal, progressing with the degree of the latter (Himmelsbach, 1934). This is a simple index of addiction liability, which is positive for dilaudid and codeine as well as for morphine and heroin. It is negative for barbiturates, acetanilid and cocaine (Himmelsbach, Gerlach and Stanton, 1935; E. J. Stanton, 1936, 1937). Joel and Ettinger, 1926, found that morphine habituation does not change the reactions of rats to the chloral group, or to picrotoxin, strychnine or cocaine.

Clinical appraisal of addiction liability may be done on addicts (stabilized for two weeks on a constant dosage of morphine) by the abeyance of withdrawal symptoms during the administration of the substitute, and their outbreak on its withdrawal. This has confirmed the addictant qualities of dilaudid, codeine and the various new derivatives (Himmelsbach *et al.*, 1940). It has also been attempted to test addiction by administration to hopeless cancer and tuberculosis patients as part of the regular treatment, but the results in such patients are equivocal.

Treatment of Opium and Other Drug Habits.—The primary indication is the withdrawal of the drug. This must be done under medical supervision, best in special institutions, for the patients have neither the will power nor the physical resistance to carry it through unaided; attempts at self treatment are rarely successful. Indeed, the closest surveillance of the patient is indispensable, both to prevent clandestine continuance of the drug and to control the withdrawal symptoms. When the drug has been completely stopped, for a few days, the intense craving for it disappears, and the patient may be considered as provisionally cured, although still in need of tonic treatment. Contrary to the popular impression, the withdrawal is a fairly simple problem. The chief difficulties are subsequent relapses. Re-orientation of the psychopathic personalities can not be accomplished in a few weeks, and often not at all, and the cure therefore is often not permanent. The memory of the morphine euphoria remains, and any stimulus associated with the former use of the drug is likely to evoke the old desire, and every unpleasantness suggests the means of escape (Pescor, 1938). The patients are likely to succumb again, sooner or later, and if the drug is resumed the addiction develops rapidly. It is necessary to be especially cautious in the therapeutic use of opiates on ex-addicts. About a fifth of any large group of addicts have been through repeated treatments (L. Kolb, 1936). The average duration of the "cure" is a little over two years. Only 2.5 per cent abstain for more than five years (Pescor, 1938). Those who were treated against their full consent naturally relapse with the first favorable occasion. These remarks apply also to cocaine and other serious drug habits, the treatment of which is identical. The withdrawal requires energetic and decisive procedures. It is important first to put the patient into good physical and mental condition (E. S. Bishop, 1920); then the drug should be withdrawn abruptly, or reduced rapidly, under confinement in special wards or hospitals. Gradual reduction causes probably more suffering by prolonging the struggle, and is generally unsuccessful. "Insensible" withdrawal does not exist; the sensations of the patients recognize even small reductions of dosage. Ambulatory treatment is so often inefficient, and is so liable to fraud, that it is rarely justified (S. D. Hubbard, 1920). Advertised "morphine cures" generally contain morphine and are used by addicts to supply the drug. Abrupt withdrawal and rapid reduction are equally successful, and the total suffering of the patient is about the same. The abrupt method is more extensively used for its simplicity (P. Wolff, 1928), but the preference depends considerably on the special experience of the physician. In the rapid reduction, the withdrawal is completed in five to ten days. Bishop advises to begin by reducing the number rather than the size of the doses. The details require individualization, especially if any opiate is given. Restlessness and insomnia call for sedative baths, paraldehyde, barbiturates or bromide; pains for salicylates; dextrose injections (1000 cc. of 10 per cent by vein) may be given if the patient refuses food. Purgatives and other special adjuvants are not necessary and are often harmful (Kolb, 1936). The enthusiasm of their advocates is based on inadequate controls; the majority of patients go through simple withdrawal with surprisingly little difficulty, especially when supported by the confidence of the physician.

The clinical relief of the withdrawal symptoms by drugs has been tested systematically by Himmelsbach and Andrews, 1943. Codeine was ineffective in the dosage of 26 mg., effective with 52 mg.; demerol was effective with 100 and 200 mg.; morphine with 5, 10 and 20 mg., more effective and more sustained by vein than hypodermically. *Thiamine, neostigmine, pentobarbital* and *atropine* were ineffective in ordinary doses; nor did neostigmine prevent or modify clinical morphine addiction in any manner or degree (Himmelsbach and Oberst, 1942; H. L. Andrews, 1942).

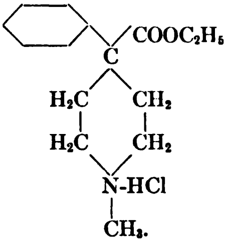
Thiamine was reported by O. G. Fitzhugh, 1939, to decrease the withdrawal irritability of addicted rats, the administration being started two days in advance. Chronic morphinism as such does not increase the requirements for thiamine in dogs (Cowgill, 1939). *Insulin* was advocated by M. Sakel, 1930 and 1933, and Anton and Jacobi, 1930, with the claim that twenty to thirty units per day permit rapid withdrawal of morphine without emesis, diarrhea and restlessness, and with diminution of the psychic symptoms. The clinical evidence is not convincing, and controlled experiments on monkeys (Seevers and Stormont, 1936) and on rats (Stanton, 1937) are quite negative. Thienes and Detrick, 1939, claim that *parathyroid hormone* hastens the dehydration and mitigates the withdrawal symptoms in rats. "*Rossium*," an antipyrine derivative, was introduced by Ostromislensky, 1935, on the basis of his unsubstantiated "anaphylactic theory of morphinism." Critical clinical tests show it to be without demonstrable benefit on the abstinence syndrome (Himmelsbach, 1937). The *scopolamine (hyoscine) and atropine treatment* was introduced by M. K. Lott, 1901 (Wagner and Riewel, 1905), to secure amnesia of the withdrawal. Kolb claims that it actually increases the suffering, leaving the patient more or less shaky for days, and with an indefinite craving that prompts relapse. It also has a high mortality, in one institution six deaths in 130 treatments. The *Lambert-Towns routine* (A. Lambert, 1913) also utilizes belladonna, with active purgation. Kolb states that it increases the suffering and is dangerous, and that its chief use is so to disable the patients that they can not escape. *Purgation*, generally by magnesium sulfate, is used in several routines, originally with the idea of eliminating some hypothetical toxic agent. It distracts the attention, but is otherwise detrimental by contributing to dehydration, as are also *nauseants*, pilocarpine and milk injection fever (P. Wolff, 1928). The withdrawal itself usually results in diarrhea, sometimes severe, for several days (Kolb).

Experimental Control of the Withdrawal Symptoms in Monkeys.—Seevers and Stormont, 1936, found that only oxygen inhalation and intravenous hypertonic glucose or sucrose gave relief. Administration of calcium, parathyroid, magnesium, potassium and insulin was ineffective. Sodium thiocyanate (advocated by Bancroft) made the animals more sick.

The *after-treatment* includes physical rehabilitation and the more difficult problems of mental and emotional stabilization and sociologic placement. It is highly important that the patient rest for several weeks or, better, months, preferably in a sanatorium. Insomnia should be relieved with bromide and barbiturate, guarding against the acquisition of a habit. The "recovered" patient must be protected as much as possible against pain and all conditions that would tempt him to resume the drug. Psychotherapy may be useful to prevent recurrence.

DEMEROL

This substance also known as *Meperidine, Isonipecaine*, and abroad as *Dolanthin* and *Pethidine*, a synthetic phenylpiperidine derivative, is a clinically satisfactory substitute for morphine, except against cough and diarrhea. The effects are not as lasting. It is not constipating, but tends to relax spasm of smooth muscle, similarly to atropine, to which it is chemically related. It produces euphoria similar to that of morphine, and prolonged administration may lead to addiction (Anslinger, 1946), but with less dependence than morphine (Batterman and Himmelsbach, 1943; Samter, 1946; Wieder, 1946; review, J.A.M.A., *132:* 43, 1946). *The provisions of the narcotic act must be observed in prescribing demerol.*



Demerol, ethyl-1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, was introduced as an analgetic by Eisleb and Schaumann, 1939.

Urinary Excretion.—Patients excrete 2 to 21 per cent, average 9 per cent, of the amount administered (300 to 800 mg.); about three-fourths within seven hours after a single dose (F. W. Oberst, 1943). It is *hydrolyzed* by liver *in vitro*, but not by the other tissues tested. The hydrolysis is inhibited by physostigmine and by fluoride (F. Bernheim and Bernheim, 1945).

Clinical Analgesia.—Oral or intramuscular administration of 30 to 150 mg. is successful and safe for practically all conditions which are ordinarily subject to morphine analgesia, including postoperative pain, preanesthetic medication, parturition, and colics. Its brief action, lasting two or three hours, renders it less convenient against cancer. *Side actions* are unimportant: Dizziness, perspiration, dry mouth are frequent, nausea and vomiting exceptional, drowsiness is brief and not followed by confusion. There are no visceral lesions. *Addiction* is frequent, and is broken more easily than morphine addiction (Batterman and Mulholland, 1943).

For preanesthetic medication, 100 mg. of demerol, hypodermically, are equivalent to 15 mg. (¼ grain) of morphine. Excessive depression occurs only half as frequently with demerol. It may be administered with 0.4 to 0.6 mg. of scopolamine (Rovenstine and Batterman, 1943). In *patients with intracranial lesions,* demerol, like morphine, may slow the respiration to an alarming degree (S. A. Guttman, 1944).

In *parturition,* demerol produces good analgesia and is relatively free from untoward effects on mother or child (W. Sonnek, 1941). The progress of labor is not disturbed, but rather accelerated by increased uterine force (Solomons and Widdess, 1943).

Demerol also has considerable local anesthetic action (E. L. Way, 1946).

Spasmolytic action has been described clinically for intestinal, biliary and ureteral colic and bronchial spasm, but the reports are discordant. In intact animals, Gruber, Hart and Gruber, 1941, observed marked contraction of the intestines; excised smooth muscle gave variable results, including slight relaxation. Fellows and Cunningham, 1942, found that several *phenylpiperidine derivatives* relax smooth muscle and inhibit histamine, pituitary and barium spasm similarly to papaverine.

Circulation.—Intravenous injection of demerol generally lowers the blood pressure by vasodilatation, even with relatively small doses (Gruber *et al.*, 1941).

Habituation.—*Tolerance* to the analgetic effects develops in patients with continued use over eight weeks, and persists for at least four weeks after withdrawal. A patient used 3 Gm. daily, hypodermically (Wieder, 1946). The response is sufficiently pleasurable and the withdrawal sufficiently uncomfortable to discourage voluntary discontinuance (H. L. Andrews, 1942). The withdrawal syndrome, typically like that of morphine, but milder and shorter, can be evoked after ten days of continued use. Demerol administration satisfies the drug hunger of stabilized opiate addiction (Himmelsbach, 1942).

PREPARATIONS.—***Demerol Hydrochloride** (Isonipecaine, Meperidine, Dolanthin); marketed as tablets of 50 mg. and as ampuls of 100 mg. in 2 cc. *Average dose:* preoperative, 100 mg. intramuscularly; postoperative, 50 to 100 mg. orally or by injection.

1,1-diphenyl-1-(dimethylamino isopropyl)-butanone-2 is a potent analgetic agent in man and in animals. It resembles morphine also in respiratory depression, slowed heart and mouse tail erection. It acts weakly on intestine and is not emetic. Dogs do not develop tolerance to the analgesia. The therapeutic oral dose, 5 mg. for man, does not produce significant side actions or euphoria (C. C. Scott and Chen, 1946).

Betahydroxy-alphabeta-diphenyl ethylamine ("*M4*" of Dodds, Lawson and Williams, 1944) has morphine-like analgetic properties and may replace morphine in cancer (200 mg. every four hours). It has a low toxicity and does not produce undesirable side actions, except some mental confusion. Like morphine, it dilates the pupils of cats and produces hyperglycemia in rabbits

PAPAVERINE AND PERPARINE

Papaverine is the most important isoquinoline alkaloid of opium. Its actions are quite unrelated to those of morphine. It is not narcotic, and is but slightly analgetic. It does not produce tolerance or addiction. It tends to relax the tonus of all smooth muscle, without interfering with the normal contractions (Pal, 1913, 1914). It was therefore suggested against spastic colic of various organs (30 to 80 mg. by mouth or hypodermically, 5 to 30 mg. by vein, Pal), but proved rather ineffective. Its toxicity is low: Bouchet claimed that 1 Gm. produced no effects on man. It decreases the tendency to cardiac fibrillation and may be used instead of quinidine.

Perparine is derived from papaverine by substituting ethoxyl for a methoxyl group. It was introduced for the same therapeutic field, but probably has little value, although it is claimed to be three times more potent in depressing smooth muscle tonus, and one-third to one-half as toxic (Pouchet, 1933). It is nonaddictant and has no effect on morphine withdrawal symptoms (Himmelsbach, 1937).

Gastro-Intestinal Tract.—Papaverine lowers the tonus level of the stomach, slows or suppresses its normal peristalsis and counteracts physostigmine stimulation. Perparine is up to twice as potent. Their effects on the intestinal movements are relatively slight and inconstant, as is also their antagonsim to the morphine tonus; but they decrease phenolphthalein diarrhea in cats (Gross and Slaughter; von Issekutz *et al.*, 1936). Stoerk, 1915, employed papaverine (60 mg. three times daily) against the tenesmus of bacterial dysentery. Excised rabbit intestine is depressed by 1:1,000,000 (Mulinos, Shalman and Pomerantz, 1939). L. W. Rowe, 1942, reports a *morpholine compound* that proved twice as potent as papaverine for relaxing excised intestine.

Ureteral Colic.—Macht, 1916, reported that papaverine relaxes the tone of the ureter, without inhibiting the peristalsis. Geraghty and Macht, 1916, suggested its injection by ureteral catheter against the colic of ureteral calculi (5 cc. of 2 per cent solution of the hydrochloride). The gallbladder and the seminal ducts are also relaxed (Macht, 1919).

Heart.—Papaverine produces dilatation of the coronary vessels and renders the dog heart less susceptible to ventricular fibrillation by faradic stimulation (Lindner and Katz, 1941) and by coronary ligation (McEachern *et al.*, 1941). It depresses auriculoventricular conduction and removes ventricular extrasystoles. Excessive doses cause intraventricular block, paroxysmal ventricular tachycardia and a peculiar ventricular fibrillation (L. N. Katz *et al.*, 1941; Wégria and Nickerson, 1942). *Clinically,* 0.1 Gm. by mouth, three or four times daily, produces significant improvement on over three-fourths of patients with anginal symptoms; 0.2 Gm. four or five times daily is useful against premature beats. It is less toxic than quinidine and has the advantage of coronary dilatation. It is not addicting (Elek and Katz, 1942; E. E. Swanson, 1945). Prolonged administration to dogs with experimental myocardial infarction reduces the size of the infarct by increasing the anastomotic channels (R. Mokotoff and Katz, 1945). It has been proposed as a *test of circulation time,* injecting 40 mg. of the hydrochloride into a cubital vein in one second. The signal is a deep inspiration, normally in sixteen to twenty-seven seconds. This is commonly followed by nitritoid symptoms (Elek and Solarz, 1942). L. Berk and Sapeika, 1945, find this test unsatisfactory. Pal reported that small doses of papaverine lower abnormally high *blood pressure,* while much larger doses are required to lower the normal pressure. Macht, 1916, claimed that it lowers blood pressure mainly by peripheral vasodilator action, especially in the splanchnic area, and that the coronary circulation is increased. The perfusion rate through frog legs is increased (Mulinos *et al.*, 1939). On the basis of these claims, papaverine was tried against *hypertension, angina pectoris* and *thrombo-angiitis obliterans,* but it appears to be unreliable (Littauer and Wright, 1939). With intravenous injection into dogs, the initial fall of pressure is succeeded by hypertension and renal vasoconstriction (Mercier, 1931); but large doses neutralize the pressor action of epinephrine (Mercier et Delphant, 1932).

Local Anesthesia.—Papaverine is somewhat anesthetic and has been used on the cornea as 4 to 10 per cent solution.

Fate of Papaverine.—It is probably extensively destroyed in the body, since neither papaverine nor any immediate decomposition products have been recovered from the organs or excreta after its hypodermic administration (Zahn, 1915).

Papaverine Hydrochloride, U.S.P., is soluble in water (1:30). Dose, by mouth or vein, 30 to 100 mg., ½ to 1½ grains. *Papaverine Hydrochloride Injection,* in water for injection; usual size, 30 mg. in 1 cc. Commercial papaverine contains considerable cryptopin, to which most of its chemical tests are due (Pictet and Kramers, 1910). In general, however, the quality of commercial opium alkaloids is satisfactory (Warren, 1915).

Tetra-Hydro-Papaveroline.—Laidlaw, 1910, found that this inhibits the tone of unstriped muscle, dilates the bronchioles and blood vessels and lowers blood pressure, at the same time stimulating the heart. It is relatively nontoxic. Marshall, 1912, tried it clinically in arteriosclerosis, but found it practically inefficient—probably because it is too easily oxidized. Exfoliative dermatitis and extensive alopecia have been reported as consequences of the prolonged use of a papaverine derivative ("*cyverine*") as antispasmodic (O. L. Levin and Behrmann, 1942).

Narcotine and Narceine are related to papaverine in composition, and their effects are similar but weaker (Pal, 1914). Narcotine prolongs the emptying time of the stomach and inhibits the movements of the intestines, but it could not be used against colic, as effective doses upset digestion (Dikshit, 1932). Its addition to morphine has probably no advantage. Macht, 1915, found, contrary to Straub, that it is quite toxic to the heart, respiration and other functions. M. Hayashi, 1931, reports on its peripheral actions and claims that it has some central depressant effect. Cooper and Hatcher, 1934, conclude that it does not appear to exert the therapeutic effects of morphine. The toxicity varies with the rate of absorption and is sixty times higher intravenously than for oral administration. Only traces are excreted by the urine, in cats.

PROTOPINE GROUP

Curare and muscular actions were described by v. Engel, 1890, for the protopine group—certain unimportant alkaloids (protopine, crytopine, chelidonine, homochelidonine and chelerythrine) which occur in opium, but especially in other Papaveraceous plants (Sanguinaria or Bloodroot); and Chelidonium or Celandine; Bocconia.

Chelidonine is the most promising member of the protopine group. It is chemically related to papaverine, containing the benzyl-isoquinoline group. It therefore depresses all smooth muscle and has a low toxicity. Hanzlick, 1915, suggested its clinical trial against spasm and colic of smooth muscle. The sulfate is freely soluble in water; it is incompatible with chloride. The dose is 0.2 Gm., 3 grains. H. Meyer, 1892, found that it produces, in frogs, descending depression of the *central nervous system,* similar to morphine, but without spinal stimulation. Mammals also respond by analgesia and sleep, without marked depression of reflexes. The respiration is unaffected by therapeutic doses; moderately slowed by larger doses. *Toxic doses* cause coma, without nausea or vomiting; finally, the vasomotor center becomes paralyzed. *Peripheral actions of chelidonine* have been investigated especially by Hanzlik, 1921. Like other isoquinoline alkaloids (narcotine, papaverine), it depresses all kinds of *smooth muscle*. The effect appears to be directly on the muscle substance, since it antagonizes not only pilocarpine, but also histamine, peptone, anaphylaxis, epinephrine and even barium; while these do not remove chelidonine depression. Anan, 1929, claims that low concentrations raise the tonus of excised intestines and uterus, while higher concentrations depress. Large doses depress *cardiac muscle*, slowing and dilating the heart. *Skeletal muscle* is also depressed (Hanzlik), and Meyer described paralysis of sensory and motor endings. It has no effect on nerve trunks, even in high concentrations.

Chelidonium juice is an acrid irritant, applied in folk medicine to remove warts. The acrid principle has not been isolated. Chelidonium also contains berberine.

Sanguinaria (Bloodroot) has been used as a nauseant, usually as the 10 per cent acidulated tincture (dose, 1 cc., 15 minims). It contains sanguinarine (reports, Council on Pharmacy and Chemistry, 1911, 60) and other alkaloids (Kozniewski, 1910). It is irritant, but requires further pharmacological investigations.

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HYDRASTIS

Hydrastis (Golden Seal), the rhizome and roots of Hydrastis canadensis, has few, if any, rational indications. It was employed empirically as a bitter stomachic; to check internal hemorrhage and locally in catarrhal conditions, especially of the genito-urinary tract.

Hydrastis was used by the Indians, mainly as a pigment, but also as medicine. It was introduced by the eclectic physicians. The plant is becoming rare, but is easily cultivated (Henkel and Klugh, 1908). The dose of dried Hydrastis is 2 Gm.; that of *hydrastine hydrochloride* is 10 mg.; *hydrastinine hydrochloride*, 30 mg. Both salts are water soluble. The alkaloids are also used locally for conjunctivitis or gonorrhea, 0.1 to 0.5 per cent. Dilute solutions of hydrastinine give a blue fluorescence.

Constituents.—Hydrastis contains at least three alkaloids: berberine, 1.5 to 4 per cent; hydrastine, at least 2.5 per cent (U.S.P.), and canadine, a derivative of berberine. There is also some resinous matter, etc.

Hydrastine is an isoquinoline derivative, closely related to some of the minor opium alkaloids, narcotine, laudanosine and papaverine. Narcotine is methoxyhydrastine, an H of hydrastine being replaced by OCH_3. Oxidation splits off opianic acid and forms analogous artificial alkaloids, *hydrastinine* from hydrastine, *cotarnine* from narcotine. *Berberine*, $C_{20}H_{17}NO_4$ (structure, Faltis, 1910), is an intensely yellow and bitter alkaloid, of wide occurrence, which gives the color and taste to a large number of "golden" roots and bark (Berberis, Xanthoxylon, Coptis, etc).

Actions of Hydrastis.—The effects of the drug and its different alkaloids are qualitatively similar.

Central Nervous System.—Hydrastine produces convulsive effects analogous to those of strychnine. These are also obtained with the fluidextract. The derivatives hydrastinine and cotarnine have a purely depressant action, producing death by respiratory paralysis (Laidlaw, 1910). There is no narcosis.

Circulation.—Experimental results indicate that the effects of hydrastis and its alkaloids and derivatives on the circulation are too uncertain to be therapeutically useful. The clinical evidence also appears insufficient to establish their value. Frey, 1909, found that hydrastinine had no effect on pulmonary hemorrhage; and Hanzlik, 1918, showed that hydrastis and its alkaloids, including hydrastinine, are not styptic on ordinary wounds, either with local or systemic administration, but rather tend to increase the bleeding. The effects of hydrastis on the circulation are variable and the descriptions of different investigators are discordant. Williams, 1908, obtained no effects with hypodermic or oral administration, even with large doses. Intravenously the fluidextract, hydrastine and berberine produced the same results: considerable fall of blood pressure, followed with small doses by a slight and short rise. With large doses, the pressure remained low. These effects were predominantly cardiac. The vasomotor center is not directly affected by moderate doses of hydrastis, hydrastine, berberine, hydrastinine or cotarnine, but may be stimulated indirectly through respiratory depression, convulsive phenomena or cardiac unrest. With toxic doses, there is vasomotor paralysis and paralysis of vagus endings. Excised organs show some vasodilation. On the scarified skin, hydrastine (1:1000) produces some blanching (Sollmann and Pilcher, 1915). *Hydrastine* is related to the protopine group and therefore depresses the cardiac and skeletal muscle, and has a weak local anesthetic action. *Hydrastinine* also causes some primary fall of blood pressure, but a larger rise (about 15 mm.) maintained for over fifteen minutes; the heart rate is slowed. This rise is also predominantly cardiac, but there is a stimulation of the arterial muscle, not prevented by paralyzing the nerve endings with ergotoxine. Kurdinowski, 1904, interprets its actions rather differently.

Uterine Actions.—Fellner, 1906, Kehrer, 1907, and Lieb, 1914, showed that hydrastis, hydrastine, hydrastinine and cotarnine increase the tonus and excite rhythmic contractions of the uterus, both in the excised organ and in living animals. This has been confirmed by the subsequent workers; also for the surviving human uterus (Rübsamen and Kligermann, 1912). High concentrations relax (Wendling, 1915). Berberine has similar effects (Marek, 1911). La Torre, 1912, examined histologically the uteri of animals treated with hydrastinine. The muscular layers were contracted and thickened, compressing the larger vessels, and thereby probably decreasing the blood supply of the mucosa. Laidlaw found the stimulant action of hydrastinine and cotarnine constant in the excised organ, but varying with conditions during life. Hydrastis does not act on the intestine and very slightly on the bladder. Synthetic hydrastine appears to be rather more stimulant than the natural alkaloid (Wendling, 1915). The *bronchioles* are not markedly affected in pithed animals (D. E. Jackson, 1914).

Actions of Berberine and Canadine.—Berberine acts as a simple bitter in small doses. Its bitter taste and the yellow stain which it produces on linen render it objectionable in the therapeutic use of hydrastis. Berberine is about seven times as active as hydrastine on the circulation; and as hydrastis contains about one and one-half times as much berberine, about 85 per cent of the circulatory effect is due to this alkaloid. Large doses lower the temperature, increase peristalsis and kill by central paralysis (Curci, 1892). It is not excreted, being probably oxidized completely (Berg). The actions of berberine have been reviewed experimentally by R. N. Chopra, Dikshit and Chowhan, 1932. It is a feeble local anesthetic. Intraspinal injection produces motor paralysis. Intraperitoneal injections into trypanosome-infected rats prolong life somewhat (Seery and Bieter, 1940).

Canadine resembles morphine somewhat in its action. It is present in too small a quantity to be of practical importance. It occurs also in xanthoxylum, where its actions have been studied by Laidlaw, 1913.

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COTARNINE

Cotarnine salts (marketed under the name of *stypticine* and *styptol*) were tried locally and systemically to arrest bleeding, especially in menstrual disorders. Their employment was based on weak clinical and experimental data, which do not stand critical examination.

Use against Hemorrhage.—Hanzlik, 1918, showed that cotarnine is not a local hemostatic. Systemically, it tends to lower blood pressure, and thus somewhat decreases bleeding.

General Symptoms.—K. Mohr, 1905, found that small doses produce only some lassitude and drowsiness. Larger doses had a pronounced sedative action, especially in cats and dogs. Ataxia was also marked. With fatal doses, these effects were followed by some excitement, then progressive paralysis till death. Toward the end, the respiration became slow and shallow, sometimes interrupted by asphyxial convulsions. Laidlaw, 1910, describes indefinite depression of the central nervous system and death by paralysis of the respiratory center. Relatively small doses slowed the respiration without change of depth.

The *fatal dose* ranges from about 0.1 Gm. per kilogram for guinea pigs (Laidlaw) to 0.3 to 0.4 Gm. per kilogram for rabbits, and even higher for dogs and cats (Mohr).

Uterine Contractions.—Kehrer, 1907, reported that cotarnine stimulates the uterus, excised and *in situ*, pregnant or nonpregnant, increasing the contractions and tonus. This has been confirmed for the excised organ by all subsequent workers (Lieb, 1914). The results *in situ* are contradictory. Chiappe and Ravano found that the pregnancy of guinea pigs was not affected by toxic doses; and that even fatal doses produced no uterine abnormalities. The *clinical data* are in harmony with these negative results.

Other Smooth Muscles.—Offergeld quotes contraction of the intestines and bladder; but Laidlaw found the bladder irresponsive.

Systemic Circulation.—Intravenous injection produces variable changes in the blood pressure; sometimes a fall; or a momentary fall followed by a slight rise (Kehrer, 1907; Laidlaw, 1910; Lieb, 1914). If the vagi are divided, the rise is more prominent (Pilcher and Sollmann, 1915). The vasomotor center is not affected directly, but may be stimulated by the slowed respiration (Pilcher and Sollmann); this probably accounts for the rise. The fall of pressure appears to be cardiac; for the Langendorff heart is slowed and weakened (Laidlaw). This diminished output of the heart has been credited with causing a hemostatic effect; there is no evidence that it occurs with therapeutic doses; and even with the experimental doses it is too slight and too evanescent to influence a persistent hemorrhage.

Direct action on systemic arterioles seems to be absent, either with systemic administration or on perfusion with reasonable concentrations (Laidlaw; Mohr).

Coagulation of blood is not affected, whether the cotarnine is added directly to the blood or injected into the animal (Laidlaw; Marfori).

Dosage and Administration.—The cotarnine salts are used by mouth or hypodermically. The intramuscular dose is 0.25 to 0.5 Gm., as 10 or 20 per cent solution, repeated daily as needed. The injections are not irritant. By mouth, the dosage is from 0.05 to 0.1 Gm. four to five times daily.

Side Actions.—None have been reported from oral administration or from hypodermic injections of 0.5 Gm. Offergeld found some lassitude with 0.7 Gm. and a single case of temporary collapse with 0.65 Gm. by intramuscular injection.

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BENZYL BENZOATE AND OTHER BENZYL ESTERS

Benzyl benzoate and acetate were found by Macht, 1918, to *relax excised smooth muscle* from various organs. They were tried clinically in colics or spasmodic conditions of smooth muscle (1 to 10 cc. of a 20 per cent alcoholic solution in cold water, three to four times daily), especially in functional dysmenorrhea (Litzenberg, 1919) and in hypertension. Thorough investigation showed that clinical doses, by mouth, are entirely without effect (Gruber, 1924). Larger doses (also of benzyl alcohol) produce only local irritation, *i. e.*, vomiting and diarrhea (Gruber, 1923; bibliography). If injected parenterally, the benzyl compounds depress the heart and the respiration, and increase the urine flow (Gruber, 1925), without depressing the smooth muscle in those organs against whose overactivity the drug has been especially advised, *i. e.*, the uterus, intestines, stomach and bronchi (Mason and Pieck, 1920). The *toxicity* of the benzyl esters is low, since they are converted into hippuric acid. Dogs tolerate considerably more, by mouth, than do rats, rabbits and cats (B. E. Graham and Kuizenga, 1945).

The earlier reports of beneficial results in dysmenorrhea can probably be explained by suggestion. The application of a mixture of equal parts of benzyl benzoate, soft soap and isopropyl alcohol against *scabies* has been advised (Kissmeyer, 1937; A. H. Slepyan, 1944). D. C. Daughtry, 1945, reports rapid cures with 25 per cent emulsion. It may produce local irritation, and patients should be warned to discontinue the treatment if the rash or itching becomes worse. Persistent sensitization to wool follicular dermatitis not infrequently follows repeated (not single) treatments (S. J. Shane, 1946). A 5 per cent emulsion applied to clothing protects against the mites of scrub typhus.

The soluble sodium salts of the benzyl esters (sodium benzyl-succinate and sodium di-benzyl-phosphate) are also ineffective by mouth, in clinical doses. Larger doses, administered parenterally to animals, generally depress the respiration and raise the blood pressure (Gruber, 1925). The rate of *hydrolysis* by alkalis would be of some importance for the local effects in the intestines and for absorption. Volwiler and Vliet, 1921, found the amount of hydrolysis in four hours to be 3 per cent for the salicylate; 15, 18 and 23 per cent for the benzoate, stearate and cinnamate; 40, 50 and 60 per cent for the acetate, succinate and fumarate.

Benzyl Benzoate, U.S.P., $C_6H_5COOCH_2C_6H_5$, is a colorless, oily liquid, of faint odor and disagreeable, sharp taste. Insol. in water or glycerin; freely sol. in alc. and fat solvents. Best prescribed as the commercial 20 per cent alcoholic solutions or emulsions, usually flavored with aromatics (Spir. Anise). Dose, 1 to 10 cc. (¼ to 2 teaspoonfuls) of the 20 per cent solution, in cold water, three or four times daily. *Benzyl Benzoate Lotion,* U.S.P., a 25 per cent emulsion, with triethanolamine.

Benzaldehyde, C_6H_5CHO, an oily liquid with the odor of bitter almonds, also relaxes smooth muscle and is a rather feeble local anesthetic (Macht, 1919), as it oxidizes rapidly to benzoic acid in watery solutions. Its dose is stated as 0.03 cc., ½ minim.

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CANNABIS

The flowering tops of the pistillate hemp plant, Cannabis sativa, contain resinous constituents (cannabinol) which produce a peculiar psychic exaltation. As "hashish," cannabis is employed as an inebriant in the Orient, and as "marihuana" cigarettes in Mexico and Brazil and to an increasing extent in the United States. Therapeutically, it was used as an adjuvant to other drugs in nervous headaches, and as a coloring agent for corn remedies. The drug is of uncertain activity, and has no rational indication.

The **effects on man** are identical for oral administration (about 2 grains of the solid extract) and for smoking. The inebriation sets in rather abruptly, after a latent period of about an hour, in which there may be temporary digestive phenomena, anorexia, dryness or burning thirst. The phenomena differ in kind as well as in degree according to the individual personality and disposition, the surroundings and the mental preparation. *The emotional sphere* develops euphoria, expansiveness and gaity, less commonly anxiety. Waves of exaltation sweep over the consciousness and may alternate precipitously with fear and terror. The subject is likely to be quarrelsome and violent if crossed. In *the subjective sphere,* a feeling of unreality is among the first effects, with a consciousness of double personality. Objects and sensations appear exaggerated in size and in degree, the limbs are lengthened, the head is swollen, the body alternately light and heavy, time enormously lengthened. *Motor excitement* and restlessness vary in different persons; tremors of the tongue and fingers, and muscular rigidity may occur. The *pupils* become widely dilated and barely react to light. The eyes appear glazed, the conjunctiva congested, the lids reddened. The pulse is generally rapid, with marked palpitation. *Mental confusion* may deepen to visual illusions and hallucinations. The imagery is likely to become terrifying in the dark. Aphrodisiac desire, rather than impulse, occurs in some and not in others. The *after-effects* are generally light. The exaltation is succeeded by irritability and somnolence, and after some hours by sleep, from which the subject awakens hungry and thirsty, with a clear recollection of the episodes. *Toxic doses* cause vertigo and collapse, with soft arrhythmic pulse, and blood concentration sometimes to 50 per cent. Serious poisoning is rare, since the margin between the effective and fatal dose is wide; the intravenous fatal dose for dogs is a hundred times the narcotic dose.

Addiction to cannabis is usually casual, since psychopathic individuals tend to drop it for a more potent narcotic. It generally takes the form of an occasional hedonistic indulgence, whose chief harm lies in the introduction to more serious addictions. No relation to criminal offenders, sexual or other, has been established. Physical consequences are no more significant than with tobacco; digestive disturbances and marasmus are not prominent. Conjunctival congestion is common. There is apparently no material tolerance, either in man or in animals, nor are there withdrawal symptoms, except, perhaps, in extreme cases. *Insanity* is a rare sequel, and the cannabis is probably only a provocative agent that unveils the latent psychopathy. Psychopathic patients react to cannabis like normal individuals, but usually become more self absorbed and less communicative, in contrast to their response to cocaine and amytal.

Comprehensive descriptions of the effects of cannabis are given in R. P. Walton's book, "Marihuana," Lippincott, 1938; in the review of W. Bromberg, 1939, and S

Loewe, 1944. The psychiatric complications of continued use are reviewed by H. J. Anslinger, 1943, and in a clinical study by Allentuck and Bowman, 1942. The use of cannabis *in the Orient* presents a rather different picture, depending on national differences of temperament, mentality and culture, which determine different psychic reactions and "dreams." Six to eight pipes daily do not seem to produce serious consequences in hemp smokers of Northern Africa. The most deleterious results are seen in those who use the concentrated resin ("charas"). Dementia is exceptional even in advanced cases; but release of subconscious impulses may lead to violence, aggressive mania, suicide, etc. (R. N. Chopra, 1942). Withdrawal reactions are relatively mild. Cannabis is not truly aphrodisiac even in Oriental users; a few may experience psychic sexual excitations, but not physical. The addicted generally lose libido; "they are content with their pipe and their pot" (J. Bouquet, 1944). The smoking of cannabis under the name of Dagga by the *natives of South Africa* is discussed by Watt and Breyer-Brandwjik, 1936, citing a thesis of Bourhill, 1913. Native boys begin at eight or ten years, much as white boys begin cigarettes. Adolescents smoke for good fellowship rather than for the effects. The habit becomes fixed in adults, who now smoke for effect, with some craving, chiefly restlessness, on withdrawal, never as strong as with morphine or even alcohol addiction. With old age, the addiction has become ingrained.

Electroencephalograms during marihuana smoking show marked increase in the number and amplitude of the fast waves, but these appear to be of muscular, not nervous, origin (Wikler and Lloyd, 1945).

The effects on animals are also narcotic and are used for *bio-assay*. Dogs are most suitable for the general inebriation, which may be induced by oral or intravenous administration; the drug is not sufficiently absorbed from hypodermic injections. The animal becomes quieted at first, then apprehensive, and then develops static *ataxia* on standing, swaying as in the Romberg sign, standing with its legs spread to avoid falling, but it may still be able to perform complicated movements; then it becomes unable to stand alone, and finally to rise. This is succeeded by deep and prolonged sleep, during which the sensation of pain is much diminished, while the reflexes persist. Some animals show acute mania. The response of different dogs varies and must be checked against a known standard (Houghton and Hamilton, 1907, 1908; Walton *et al.*, 1938). The ataxia is the best criterion of potency, if the assay is properly performed on standardized dogs. Their tolerance is neither increased nor diminished by numerous administrations (S. Loewe, 1944; general discussion of bio-assay methods).

The ataxia in dogs is the most specific action of cannabis. It resembles that occurring after excision of the cerebellum. It is best observed in dogs, but occurs also in cats, and less typically in rabbits, monkeys and mice. It is considerably increased by amphetamine; it is not affected by amytal. *Scratching* is also a characteristic symptom in dogs. *Corneal anesthesia* in rabbits (on intravenous injection, not on local application, and not observed in dogs) was proposed as an assay method by Gayer, 1928. Reflexes in other locations are not abolished by cannabis. Psychic alterations have not been established for animals. The *Beam test*, an alkali color reaction, does not parallel the activity and has led to erroneous conclusions (S. Loewe, 1944).

Historical.—The Oriental use of cannabis as an intoxicant antedates recorded history, the tops or resin being made into a confection or smoked with tobacco. The Greek and Latin name cannabis is said to be derived from the Assyrian Kunnapu, and "hemp" is formed from the same root. It is known as Indian Hemp, Hashish, Bhang, Guaza, Gangja, Charas and Momeka. The name "marihuana," given to it in Mexico and Latin America, is said to be derived from maraguango, signifying an inebriant plant. Cannabis was introduced into therapeutics by Aubert-Roche, 1839, O'Shaughnessy, 1843, and Moxeau de Tours, 1843. Its use as an inebriant was rare in the United States before 1918 and did not become extensive until the last decade. Over 195 tons were confiscated by the Treasury Department in 1935. The hemp plant thrives practically in any climate and has long been cultivated in the Central States for its fiber and seed, but its narcotic properties were not generally known to the farmers until its recent notoriety.

The potency of the hemp plants is greatest in the resinous material exuded by secreting glands. It is much more abundant in the flowering tops than in the leaves. According to tradition, the female plants are more active; but in this country there is not much difference. The potency is said to decrease during the ripening of the seed, but this is also questioned. Hempseed contains an insignificant quantity of active substance. Hemp fiber is quite devoid of activity (Loewe). The hemp for fiber is marketed before the flowers are fully developed, and when the potency is low. The activity varies chiefly with the heredity of the plant, but environment has some influence. Plants grown in a dry, hot atmosphere, as that of certain regions of East India, are generally about twice as potent as those grown in America (Houghton and Hamilton, 1907, 1908; Walton *et al.*, 1937; S. Loewe, 1944). Different samples, however, vary considerably, and that used pharmaceutically is assayed on dogs for narcotic ataxia (U.S.P. IX). Experienced smokers in East India assay it subjectively with surprising accuracy (Chose and Bhattarcharji, 1935). The crude drug may lose activity quite rapidly (three-fourths in a year), but the extract and fluidextract are fairly stable (H. C Hamilton, 1913; Walton, 1938).

The active constituents of cannabis resin have been isolated by Roger Adams, 1940 (review, 1942), with identification of their chemical structure, as closely related aromatic derivatives. The most important are the isomeric *tetrahydrocannabinols*, which are solely responsible for the psychic actions in man and the ataxic effects in dogs (S. Loewe and Modell, 1941). They are chemically intermediate between two products that constitute the bulk of the resin-oil: the labile cannabidiol and the stable cannabinol. *Cannabidiol* determines a synergistic hypnotic action in mice. Cannabinol is not materially concerned in any of the characteristic actions. It has a feeble ataxic action on dogs (S. Loewe, 1945). The corneal anesthesia of rabbits is due to an undetermined constituent. Numerous synthetic cannabinol derivatives have been synthesized and examined. Many are active, but not as potent as the natural tetrahydrocannabinols (R. Adams, Loewe *et al.*, 1942; Alles, Haagen-Smit *et al.*, 1942; C. K. Aldrich, 1944). Cannabis also contains a volatile oil (terpenes), paraffin, pitch, etc., which are not concerned in its action. There is no specific alkaloid, but the extracts may give alkaloid reaction from the formation of choline and trimethylamine. These are not connected with the action. The fresh extract has a beautiful green color (if prepared without excessive heat), due to chlorophyl. The active principle is completely extracted by alcohol, but is insoluble in water.

The Extract (dose, 15 mg., ¼ grain) and the Fluidextract (dose, 0.1 cc., 1½ minims) were formerly in the U.S.P. The extract was about twenty-five times as strong as the fluidextract.

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PEYOTE (MESCAL)

"Peyote," misnamed "mescal buttons," consists of the tops of a small narcotic cactus, Lophophora williamsii (formerly Anhalonium lewinii), which grows in the Rio Grande region of the United States and Mexico. In Mexico "peyote" refers also to a number of other plants of varying kinds, which has resulted in much confusion (R. E. Schultes, 1937). It is dried and eaten by the Indian tribes of the Southwest in religious ceremonials, for the sense of well-being which it induces and sometimes to promote trances and hallucinations. Since 1885 the cult has spread extensively among the Negroes.

Blair, 1921, claims that the Indians are also using it as a habit drug, but Safford, 1921, states that its usage is still entirely ceremonial. Schultes, 1937, reports that the Indians consider it a panacea for practically all illness "as the White Man uses aspirin."

The cactus contains eight alkaloids structurally related to hordenine and the epinephrine series. They have been synthesized. Their actions differ somewhat (Lewin, 1888). Several are sedative. The most important is *Mescaline* (trimethoxyphenyl methylamine), which produces peculiar psychologic disorientations, with hallucinations of the special senses, particularly flashes and lines of ever-changing brilliant colors. They appear the same in both eyes and are therefore central (Dixon, 1899). A psychologic study of mescaline hallucinations was made by Knauer and Maloney, 1913. Waeber, 1912, failed to find the described visual and auditory effects and double personality, but observed other psychic and physical disturbances. Bresler, 1905, experimented with its actions on mentally deranged patients. E. Guttmann and Maclay, 1936, who administered small doses (0.1 to 0.2 Gm.) of the synthetic alkaloid orally to psychotic patients, classify the effects as depersonization (confusion of personality), derealization (unreality of environment) and hallucinations similar to those in schizophrenia. Mescaline and its related compounds produce a number of *other effects*, including fall of blood pressure (prevented by vagotomy or atropine), motor paralysis by depression of the central nervous system and death by respiratory failure (G. S. Grace, 1934). *Pellotine*, one of the alkaloids, was investigated by Pincussohn, 1907. *Anhaline* seems to be identical with hordenine (Spath, 1919). Mescal is not used therapeutically.

"Cactus."—Preparations from the cactus Cereus grandiflorus have been used as substitutes for digitalis, particularly in functional cardiac neuroses. Proprietary preparations have been widely advertised. Experiments on animals and men have shown them devoid of digitalis and strychnine actions and indeed absolutely inert. The clinical testimony is not conclusive. Careful observers have failed to find any clinical effects; those who describe positive results have perhaps undervalued the element of suggestion in the treatment of functional neuroses (report, Council on Pharmacy and Chemistry, 1910; J.A.M.A., *54:* 888).

The drug was introduced in 1864 by Rubini, a homeopathic physician. Boinet and Teissier, 1891, described a weak digitalis action on the frog's heart, produced by an alkaloid, which they considered derived from Cactus grandiflorus. They were evidently working with some other substance. No serious attempts were made to check on the extreme claims for the cactus preparations, until Hatcher, 1907; Matthews, 1908; Lyon, 1910; and Hatcher and Bailey, 1911, showed that even enormous doses of the best known preparations are practically inert—entirely so when given by mouth—in animals and in man, in health and in disease. Gordon Sharp, 1894, also found the clinical results negative when the genuine drug was used. The favorable clinical literature (summarized by Hatcher and Bailey, 1911) does not bear stringent criticism. Some of the discordant statements are probably due to *confusion with other cacti*. No alkaloid or other definite principle has been demonstrated in the grandiflorus, but alkaloids have been isolated from a number of cacti (Heffter, 1898): mescaline, anhalonidine, pellotine, pectenine, pilocereine, etc. Mogilewa, 1903, investigated their action on the heart and found that they produce slowing, without decrease of pulse volume (in contrast to digitalis).

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HARMALINE ALKALOIDS

Harmine is an alkaloid of the seeds of Peganum harmala, a plant growing in the steppes and wild places of the Mediterranean and East Indian belt, used since antiquity for a variety of conditions, especially as anthelmintic (review, J. A. Gunn, 1937). It is identical with *"banisterine,"* isolated from a South American liana, Banisteria *caapi*, which the natives of Guiana make into a mildly narcotic beverage, used in ceremonials and reported to produce visual hallucinations and dreams, at first pleasant, then horrifying (A. L. Chen and Chen, 1939). Several derivatives (harmol, harmalol, harmaline) act similarly. Harmaline constitutes about two-thirds of the alkaloid content of harmala seed. The chemical structure is related to quinine, and these alkaloids are toxic to amebae and protozoa and somewhat antimalarial. Harmaline acts on ascaris similarly to santonin (Flury, 1911).

Harmaline is used to relieve the tremor and rigidity of the postencephalitic *parkinsonian syndrome*, when they are referable to functional cerebral depression (Lewin, 1928; Beringer, 1928). Eichler, 1929, reported a favorable but transitory effect on voluntary motion and on the rigidity of the orbicularis muscle, but no effect on the tremor, salivation, seborrhea or on myotonic tics; nor does it produce euphoria like the hyoscine drugs. The mechanism is not fully explained. The improvement was attributed to cortical stimulation, with better regulation of the impulses and therefore better control of the movements. However, the action of harmine appears to be on subcortical centers, for it produces its typical motor and psychomotor effects (but not the convulsions) in cats whose cerebral hemispheres have been excised by two stage operation (A. G. Beer, 1939). It is ineffective clinically if there is extensive anatomical degeneration. Doses of 20 to 40 mg., hypodermically, are well tolerated (Dohmann, 1929).

The harmaline alkaloids produce a variety of central and peripheral actions, which have been investigated especially by J. A. Gunn and his associates, 1931. In mammals, they cause hallucinations (Lewin, 1928), tremors and clonic convulsions. They also excite the region of the pons which results in the swimming and running movements and stiffness of the extremities (M. Sato, 1935). Central motor paralysis predominates in frogs. Small doses raise the blood pressure and stimulate the respiration. Large doses depress the heart. Fatal doses intravenously kill by cardiac depression; hypodermically, by paralysis of respiration. Strong solutions produce contraction of skeletal muscle. Intestinal muscle is relaxed. The uterus is stimulated if relaxed, and always in intact animals; but high tonus in excised uterus is relaxed. The actions of various alkyl derivatives were studied by Elphick and Gunn, 1932. The relations of the actions of the chemical structure are discussed by Gunn, 1935.

Pukateine.—This alkaloid, prepared from the Pukatea tree of New Zealand, is a phenanthrene derivative. Its chemical structure is related to that of bulbocapnine and apomorphine, but its actions, studied by W. S. Fogg, 1935, are closer to those of morphine, and include analgesia and sleep (10 mg. in man). Large doses produce hyperexcitability toward abrupt stimulation, and death is preceded by convulsions similar to those of strychnine. The respiration stops before the heart.

Peripheral Actions.—Smooth muscle is generally depressed. The *heart* is slowed in mammals and frogs, partly by vagus stimulation, but chiefly by direct depression of the cardiac muscle, prolonging the refractory phase. It renders the ventricles more resistant to fibrillation by faradic stimulation. Perfused *blood vessels*, including the coronary, are dilated. The *blood pressure* falls even with small doses.

Khat.—The Khat habit among Oriental people consists in chewing the leaves of Catha edulis (Celastraceae), grown in Abyssinia, Arabia and Somaliland. They are also used as a tea. The leaves contain three characteristic alkaloids, with somewhat indefinite actions (R. Stockman, 1913).

Piscidia (Jamaica Dogwood) produces ataxia similar to that of cannabis (Pittenger and Ewe, 1919; *bio-assay*), and was introduced as a sedative, hypnotic and analgetic (Ott, 1883; Nagle, 1881). It is practically useless, however (Tyrode and Nelson, 1905). It contains a crystalline nonnitrogenous principle, "piscidin"; but this does not seem to be the bearer of the ataxic action (Pittenger and Ewe). Hauschild, 1936, reports on its toxicity. Death occurred by respiratory paralysis, with convulsions.

Lactucarium.—The dried milk juice of wild lettuce, Lactuca virosa, was introduced by Dr. Coxe of Philadelphia in 1799 as a sedative. The average dose is 1 Gm., 15 grains. Lettuce had some reputation as a hypnotic in ancient times, but it is probably undeserved. Kelterborn took 12 Gm. of Lactucarium without any effects. No active principle has been determined.

Lupulin and hops act as bitters and have some popular but exaggerated reputation as hypnotics. The average dose of hops is 2 Gm., 30 grains; of lupulin, 0.5 Gm., 8 grains. Hops are the dried pistillate flowers of Humulus Lupulus. The active principles are contained in small glands, which can be separated as a powder, and constitute the *Lupulin.* Two acids (*α- and β-lupulinic acids*) are present. They stimulate the respiratory and vagus centers; this is followed by depression. They also depress the cardiac muscle. Lupulin contains a further, unknown constituent which is insoluble in water and is a strong cardiac poison. Power, Tutin and Rogerson, 1913, also found a trace of alkaloid. All these, however, are not active when administered by the stomach and are therefore not concerned in the action of the drug.

Loco Disease.—Horses, cattle and sheep on the Western stock ranches are subject to a peculiar disease which bears some resemblance to drug habits. The symptoms consist in motor incoordination, forced movements, misjudgment of distance, stupidity, apparent hallucinations. In the chronic form there is emaciation. Death is preceded by coma and convulsions. The cause of these conditions is obscure. It is generally attributed to feeding on certain leguminous plants ("loco weeds"—especially Astragalus). C. D. Marsh, 1909, claimed to have reproduced the condition experimentally by long-continued feeding with these plants, but H. T. Marshall, 1914, considered the results inconclusive. Later work shows that the loco weeds thrive in areas with high selenium content in the soil, and raises the question of the share of this element in the symptoms (see Selenium in the Index)

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LOCAL ANESTHETICS

Many substances of widely different chemical structure abolish the excitability of nerve fibers on local application, in concentrations which do not cause any permanent injury, and which may not affect other tissues. Sensory nerve fibers are most susceptible, so that these agents produce a selective sensory paralysis, which is utilized especially to suppress the pain of surgical operation. This property was first discovered in cocaine, but because of its toxicity and addiction liability, this has been largely displaced by synthetic chemicals. The oldest of these, procaine (novocain), is still the most widely used. Its relatively low toxicity renders it especially useful for injections, but it is not readily absorbed from intact mucous membranes and is therefore not very effective for them. Many of its chemical derivatives are also used. These and others have a changing vogue. They differ in penetration, toxicity, irritation and local injury as well as in duration of action and potency. Absolute potency is not so important for practical use as is its balance with the other qualities. If cocaine is absorbed in sufficient quantity, it produces complex *systemic actions*, involving stimulation and paralysis of various parts of the central nervous system. These are mainly of toxicologic and scientific interest. Its continued use leads to the formation of a habit, resembling morphinism. This is not so with the other local anesthetics.

Historical.—Cocaine is derived from the leaves of Erythroxylon Coca, a tree indigenous to Peru, Chile and Bolivia. It is now cultivated in other tropical countries. The leaves were chewed by the Incas of ancient Peru, chiefly in religious ceremonials, and prohibited to the common people. Their use spread rapidly after the Spanish conquest. It is now almost universal among the natives of the mountain districts of Peru, Bolivia and northern Argentina, who value their "ration" more than wages. It is popularly believed to be indispensable for strenuous labor at high altitudes, relieving fatigue and hunger. It has extended into the cities, including those of Equador, Chile and Colombia. The number of coca chewers is estimated as eight millions, almost exclusively of Indian race (Gutiérrez-Noriega, 1944; P. J. O. Wolff, 1940). In East India it is combined with the chewing of betel (Chopra, 1931). In Europe, trials with the leaves gave disappointing results. The discoverers of cocaine (Woehler; Niemann and Lossen, 1860) described its benumbing action on the tongue, without realizing its significance. As late as 1880 a British medical commission reported on the drug as merely a poor substitute for caffeine (J. U. Lloyd, 1911, "History of Vegetable Drugs"). In the same year, Anrep subjected cocaine to a more thorough pharmacologic investigation. In 1884 the Vienna oculist K. Koller was engaged in pharmacologic experiments with cocaine, and it occurred to him that the numbing effect on the tongue is anesthesia. Realizing the potential importance of local anesthesia, he tried the cocaine immediately on the eyes of animals, and then in the clinic, and announced the discovery to the German Ophthalmologic Society (Koller, recollections, 1941). Its practical value was at once generally recognized. Einhorn in 1899 (Annalen d. Chemie) demonstrated the production of local anesthesia by esters of aminobenzoic acid, and in 1905 introduced procaine (novocain). The history of local anesthesia in dentistry is described by Tainter, 1940. Prurifacients are used by West African natives to obscure the pain of circumcision and tribal scarification (G. W. Harley, 1941).

Peripheral Nerves.—Direct contact with cocaine, procaine and most of the other local anesthetics paralyzes all forms of nervous tissue, without preceding stimulation. The susceptibility of the various nerve fibers presents marked and characteristic quantitative differences. Sensory fibers are most easily attacked. By using appropriate dilutions, the paralysis is as complete as if the nerve fibers had been severed with a knife. If the drug is washed away, or absorbed, the nerve recovers its functions promptly and completely (but very strong solutions of cocaine may produce neuritis and permanent paralysis). Since these effects are strictly local, the anesthetic agent must be applied in such a way that an effective concentration reaches the nerve supply of the part which it is desired to affect. This may be accomplished by painting a solution on mucous membranes (from which cocaine is very readily absorbed); or by injecting it into or under the skin (infiltration and subcutaneous anesthesia); or around or into the nerve trunk (peri- or intraneural anesthesia); or around the spinal nerve roots (subdural or spinal anesthesia). The intact skin is practically impermeable even to cocaine, although this penetrates slightly if the skin has been macerated (Macht *et al.*, 1916).

Comparison of anesthetic efficiency may be attempted by a number of experimental methods. In transferring the results to clinical problems, the conditions of the clinical use must be borne in mind (Sollmann, 1918).

Intracutaneous injection (the "wheal" or "quaddel" method of H. Braun), observing either the duration or, better, the threshold values of the anesthesia, reproduces practically the conditions of *infiltration and of injection anesthesia.* When combined with epinephrine, it also measures absolute anesthetic efficiency. The ratio by this method is as follows:

Effective Percentage	*Intracutaneous Injections*	*Efficiency Ratio*
$\frac{1}{32}$	Cocaine, procaine, tropacocaine, and alypin hydrochlorides	1
$\frac{1}{16}$	Beta-eucaine and apothesine hydrochlorides	$\frac{1}{2}$
$\frac{1}{8}$	Quinine-urea hydrochloride	$\frac{1}{4}$
$\frac{1}{4}$	Antipyrine, potassium sulfate	$\frac{1}{8}$

The susceptibility of different skin areas varies, even in the same neighborhood, so that discordant results are sometimes obtained. The solutions should be approximately isotonic (3.5 per cent or higher, corresponding to 0.55 to 2.5 per cent NaCl). Stronger and weaker solutions are first irritant, then anesthetic, even when indifferent salts are used (Braun, 1914). A method of hypodermic standardization by dogs is described by Pittinger, 1921. Loewe, 1936, utilizes the *pseudohernia* reaction (depression of postural reflex tonus).

Mucous Membranes.—The skin of the frog's foot is most convenient; but rabbit's cornea (or guinea pig cornea, Chance and Lobstein, 1944) corresponds more closely to clinical conditions. It must be remembered, however, that the absorbability, and therefore the ratios, would differ for various mucosae. The results on the cornea are as follows:

Percentage	*Rabbit's Cornea*	*Efficiency Ratio*
½	Cocaine and phenacaine (holocaine) hydrochlorides	1
1	Beta-eucaine hydrochloride	½
2	Tropacocaine, alypin and quinine-urea hydrochloride	¼
4	Apothesine hydrochloride	⅛
8	Procaine hydrochloride	1/16
10	Antipyrine, KCl	1/20

Modifications of the methods for testing local anesthesia on rabbit's cornea and on the frog's sciatic are described by Rider, 1930.

Sensory nerve fibers of frogs may be tested through reflexes. The results correspond to the conditions of "nerve blocking." (Sixty seconds' immersion seems to give the best comparative results; Munch *et al.*, 1933.)

Percentage	*Sensory Reflex*	*Efficiency Ratio*
¼	Cocaine, procaine and tropacocaine hydrochlorides	1
2	Quinine-urea hydrochloride	⅛
8	Antipyrine	1/32

Paralysis of the motor fibers of the excised nerve trunks of frogs gives concordant results, especially when evaluated by nerve action potentials (Bennett *et al.*, 1942). The absolute values cannot be transferred to sensory paralysis, but the ratio of potency is similar.

Percentage	*Motor Fibers*	*Efficiency Ratio*
⅛	Cocaine, procaine and tropacocaine hydrochlorides	1
¼	KCl	½
1	Quinine-urea hydrochloride and antipyrine	⅛

Spinal anesthesia may be compared on frogs (Bieter and Brown, 1934).

Selective Action on Motor and Sensory Fiber.—When a ½ to 2 per cent solution of cocaine is injected into a mixed nerve or into the subdural canal, the selective action is marked, so that there is complete anesthesia without motor impairment (Alms, 1886). If the contact is prolonged, by stopping the circulation, or if stronger solutions are employed, the motor fibers become paralyzed, so that the difference is merely quantitative. A similar difference in the susceptibility of motor and sensory structures exists also for the alcohol group, aconitine, phenol, hydrocyanic acid and for pressure (Luedvitz); and even for the centrally acting narcotics, ether, etc. It is therefore a characteristic of nervous tissue rather than of cocaine. It is now generally accepted that the selective action in peripheral nerves is due chiefly if not entirely to the ratio of penetration, determined by *differences in the size of the myelinated nerve fibers*, especially the thickness of the myeline sheath for it follows this order closely, the smallest fibers being blocked first, the largest last (Gasser and Erlanger, 1929; Heinbecker *et al.*, 1934; A. J. Clark, 1937).

Peripheral Paralysis of Special Sense Nerves.—Cocaine and other local anesthetics abolish not only the sensation of pain, but other special sensations, if they are suitably applied. Here also there is some selection. *In the skin*, they paralyze first the vasoconstrictor reaction, then progressively the sensation of cold, warmth, touch, tickling, pressure, pain, "joint sense" (Heinbecker *et al.*, 1934). *In the nose*, they abolish the olfactory sense. *On the tongue*, they destroy the taste for bitter substances, but have less effect on sweet and sour taste, and none on salty taste When cocaine is applied to the appropriate nerves, it is found that the centrifugal *vagus fibers* are paralyzed before the centripetal; vasoconstrictor fibers before vasodilator; bronchial constrictors before the dilators, etc (Dixon, 1904).

Site of Action.—Local anesthetics paralyze the nerve fibers anywhere in their course, wherever they are brought into contact with them. When applied to mucous membranes or hypodermically, they select the portions peripheral to the main trunks, the thinner sheath of the terminal fibrils facilitating its penetration. It is unnecessary to assume a selective action on the histological sensory endings.

Nature of Action.—This appears to be functional. No structural changes have been demonstrated in the nerve fibers.

Chronaxia.—Subparalytic concentrations of cocaine raise the rheobase. The chronaxia is first lowered, then remains at a low level, and then rises. These effects occur in motor as well as in sensory fibers, but motor fibers require a ten times higher concentration (Cardot and Regnier, 1927). Different nerves show differences in the relation of rheobase and chronaxia (Fieschi, 1934). If skeletal muscle is immersed in procaine solution, indirect stimulation shows the increase of rheobase and decrease of chronaxia, but direct stimulation gives increased chronaxia and unchanged rheobase (Siems, 1933).

The oxygen consumption of nerve is decreased by cocaine, procaine and urethane, approximately in the ratio of their anesthetic concentrations; but some substances not anesthetic have the same effect (Sherif, 1930). *Carbon dioxide production in nerve* was investigated by Niwa, 1919, on frog's sciatic nerve with the Tashiro method. He found the same effects from cocaine as from the aliphatic narcotics: Subanesthetic concentrations increased the production; with anesthetic concentrations this increase was short or absent, the main phenomenon being decreased production.

Combination of Anesthetics.—The efficiency of mixtures of the local anesthetics corresponds to more or less complete summations, generally without potentiation: If solutions of different anesthetics are diluted until they are "just effective," then a mixture of any two of these solutions will also be "just effective," no more and no less (A. Schmidt, 1933; Sollmann, 1918; Rider, 1930). There would be little or no practical advantage in such mixtures.

Potassium Synergism.—Potassium salts may give considerable potentiation with the other anesthetics (A. Hoffmann and Kochmann, 1914). However, this seems to hold mainly for motor fibers and not for sensory (Sollmann, 1918). One per cent potassium chloride could be used with some advantage in place of sodium chloride for making up isotonic anesthetic solutions (H. Braun, 1913).

Alkalinization.—The addition of sodium bicarbonate increases the potency of most local anesthetics two to four times, for direct application or injection into nerve trunks, and probably for subdural injection and on application to mucous surfaces. This is due to the easier penetration of the free anesthetic bases, as compared with their salts (O. Gros, 1910; Sollmann, 1918; Rider, 1930). It does not apply to nupercaine and pontocaine, since these are precipitated by alkalinization. Acidification diminishes the potency of all (Beutner and Bradlow, 1943).

The usual solutions of the anesthetic salts may be mixed with an equal volume of 0.5 per cent sodium bicarbonate solution, without loss of efficiency, and with a saving of one-half of the anesthetic, and correspondingly smaller danger of accidents. The mixtures, however, do not keep well, and must be made just before use (Sollmann, 1918; Gwinn and Ferber, 1936). Alkalinization or buffering has *no advantage for hypodermic or intradermic injections*, since these do not require much penetration (Tainter *et al.*, 1939). For injection of the mandibular nerve in dentistry, alkalinized solution of procaine has somewhat quicker and shorter action, but the degree of anesthesia averages about the same (R. J. Boothe, 1941). Procaine base dissolved by the aid of carbon dioxide is more potent than the hydrochloride when applied to the cornea, but not for intramuscular injection (Beutner, 1939).

The *effects of temperature on local anesthesia* of frog's nerve differ for various types of anesthetics: cocaine, salicylamide and monacetine are more effective on cooled nerves; alcohol and chloral are more effective on heated nerves. This is probably connected with differences in solubility and the "partition-coefficient" (H. Moral, 1918).

Other Synergisms.—Addition of 0.1 to 2.5 per cent of *urea* to dilute procaine solutions materially increases their potency, to ten times, on direct application to nerve trunks, presumably by favoring penetration. The effect is not due to alkalinization (Guntermann, 1939). The action of local anesthetics is reported to be increased by intravenous injection of *methylene blue;* by the local application of *caffeine* or *theophylline* (Lipschitz and Weingarten, 1928); and by *milk injection fever* (Dannenberg, 1934); by morphine (Arima, 1935) and by the antipyretic analgetics (Stender, 1929). Cocaine anesthesia is said to be ineffective in tissue impregnated with *oxalic acid* (Velkers, 1935). Inflamed tissues are less susceptible to local anesthesia, probably because of their difficult penetration.

Epinephrine-Anesthetic Combinations.—H. Braun, 1903, confirmed that the anesthetic effect of cocaine injections is materially improved by the addition of epinephrine (about 1:50,000). The duration of the anesthesia is prolonged for over an hour. The effective concentration can therefore be considerably lowered, and the danger of poisoning greatly reduced. These results are due to the vasoconstriction, which practically arrests absorption into the circulation. On the other hand, the nervousness induced by epinephrine in hypersensitive individuals may make them more susceptible to cocaine collapse. The greatest field for the epinephrine combination is that of operations involving bleeding. It is useless on the intact cornea (Sollmann, 1918). Epinephrine is similarly efficient with procaine and most other local anesthetics.

Its effect is not as pronounced with stovaine, and is practically absent with tropacocaine, since 0.1 per cent of this destroys the vasoconstriction effect of epinephrine (Smyth, 1911). Beta-eucaine also counteracts epinephrine (Braun, 1914).

Epinephrine is not directly anesthetic either alone or in combination with cocaine; it does not increase the anesthetic effect when the circulation has previously been arrested, nor does it lower the threshold concentration in wheals, although the duration of the anesthesia is greater for a given concentration (Sollmann, 1918).

Local Vascular Action.—Cocaine produces vasoconstriction (blanching), probably by sensitizing to sympathetic stimulation. This action is lacking in the other local anesthetics. Procaine has practically no vascular effect; alypin, eucaine and stovaine cause some dilatation (Impens, 1905; Behr, 1934). Cocaine decreases *capillary hemorrhage;* procaine, apothesine and other synthetic anesthetics tend rather to increase bleeding.

The application of cocaine to mucous membranes, particularly the inflamed conjunctiva, constricts the capillaries and small arterioles, resulting in blanching, astringent sensation and contraction of vascular formations, such as polypi. The action is localized and thus peripheral. It occurs after excision of the adrenal glands and is therefore not due to synergism with circulating epinephrine (W. H. Crosby, 1939).

Vascular perfusion experiments (by the Trendelenburg method) have given contradictory results for cocaine. Abe, 1920, found that this depends on the species of frogs. *Procaine* added to perfusion fluid, 1:10,000 to 2:1000, prevents the vasodilating effect of acetylcholine, or of work on the hind leg of dogs or cats (Fleisch and Weger, 1938).

Antiphlogistic Action.—It was claimed by Bruce, 1913, Januschka and Bardy, 1915, and others that local anesthesia prevents the congestive and inflammatory action of mustard oil on the conjunctiva. Other workers consider the differences within the limits of experimental error (Stevenson and Reid, 1915).

General Toxicity to Protoplasm.—Cocaine is a rather weak protoplasmic poison, paralyzing all sorts of cells, without producing gross chemical changes. It is toxic to the lower forms of animal life (infusoria, etc.), but has little effect on bacteria or ferments.

Precipitation of Proteins and Astringency.—Neither cocaine nor the synthetic local anesthetics precipitate proteins; they are therefore not astringent in the ordinary sense, nor irritant (Sollmann, 1919; alypin, anesthesine, apothesine [slightly], cocaine, cycloform, holocaine, orthoform-new, procaine, propaesine).

Antiseptic Action.—Benzyl alcohol, beta-eucaine and holocaine are antiseptic; cocaine and procaine are not (Macht and Satani, 1920).

Yeast growth is inhibited by small quantities of cocaine, but larger doses accelerate it (Somoggi, 1916).

The *toxicity for earthworm and tadpoles* is not parallel to the toxicity for mammals (Sollmann, 1919).

The **practical application of local anesthetics** involves considerable art which must be learned in the clinic. It falls into two divisions: (1) surface application to the mucous membranes, especially of the eye, nose, throat and urethra; and (2) injections about nerves, in different parts of their course and distribution, from their spinal roots to their ultimate fibrils. The advantages and disadvantages in comparison with general anesthesia, and the selection of the local anesthetic agent also depend on clinical discrimination. Nervous, fearful and excitable patients often suffer severely from apprehension. This also disposes toward accidents. It may be at least somewhat quieted by sedatives (morphine hypodermically) half an hour before the operation, or by barbiturates, which also tend to prevent convulsions.

The *onset of the action* depends on the penetration into the nerve fibers, and the *duration* on the sojourn of the drug. In general, the sensation becomes blunted in a few minutes, but the anesthesia does not reach its maximum for ten to twenty minutes, and lasts ten to thirty minutes after a single application. The duration depends more on the concentration than on the total amount of the agent, so that it is more economical to use small quantities in high concentration, repeating if necessary (Sinka, 1939).

Local Ischemia.—As the anesthetic agent is absorbed and thus removed from the site of application, its local action ceases and its systemic and toxic effects start. Since most of these drugs, especially cocaine, are rapidly destroyed in the body, the systemic toxicity increases with the rapidity of absorption. It is therefore desirable and often necessary to delay the absorption restricting the local circulation by adding epinephrine. More dilute solution may thus be used, and the anesthetic effect is much more prolonged. With intracutaneous infiltration, the pressure and edema also result in ischemia. In suitable situations, the circulation may be slowed by bandages, or arrested by temporarily clamping the arterial blood supply.

Interruption of the circulation was introduced by Corning in 1885. He showed that this makes $\frac{1}{4}$ to $\frac{1}{2}$ per cent cocaine solution more effective than the 2 to 10 per cent solutions then in vogue, and that it greatly diminishes the danger of poisoning (H. Braun, 1914). Persistent ischemia itself, as by ligation of the artery, gradually induces anesthesia, but without drugs requires hours and therefore has no direct share in the ordinary application of local anesthetics.

Surface Anesthesia.—Anesthesia from intact surfaces requires that the drug must be absorbable. This practically excludes the intact skin, although nupercaine and pontocaine in aqueous or oily media are somewhat anesthetic (W. Laubender, 1939). Cocaine, butyn, metycaine and diothane are readily absorbed from mucous membranes, and are therefore efficient, but also correspondingly toxic. Procaine and apothesine are relatively inabsorbable and therefore less applicable. Alypin and beta-eucaine are intermediate, but the order of absorbability varies for different mucosae.

Ophthalmic Anesthesia.—Cocaine, 4 per cent, or butyn, 2 per cent, is applied to the conjunctiva for deep penetration, as in cataract operations; phenacaine (holocaine), 2 per cent, or butyn, 2 per cent, for surface action (foreign bodies), etc. Procaine is too feeble. Toxic manifestations are rare and slight since only small quantities are used. For infiltration, 2 per cent procaine is advised. Several of the anesthetic agents produce some *conjunctival irritation*, smarting and congestion. Cocaine blanches the conjunctiva, but cloudiness and even ulcers of the cornea sometimes follow its application; they are partly explainable by the drying, and the irritation by dust and other foreign matters not perceived on account of the anesthesia, and the abolition of the winking reflex. The protoplasmic toxicity may have a part in their production.

The *relative efficiency* of several local anesthetics for the conjunctiva was shown in the tabulation. Stovaine requires about seven times the concentration of cocaine (Regnier, 1923). The addition of epinephrine does not enhance the local anesthetic action on the conjunctiva (Sollmann, 1918). Experimental data are given by Closson, 1914. It is difficult to estimate degrees of irritation on animals.

Actions of Cocaine on the Eye.—Cocaine, applied to the conjunctiva, produces local anesthesia (which may not extend to the iris); local anemia (which extends to the iris, but not to the retina); and submaximal dilatation of the pupil by peripheral sympathetic stimulation. Mydriasis occurs also on systemic administration. The accommodation is impaired, but the light reflex is preserved; there is some exophthalmos. The intra-ocular pressure is usually lowered, but may be increased. The mydriasis and its associated phenomena are not produced by most of the cocaine substitutes.

A single application of 2 per cent cocaine produces complete anesthesia of the conjunctiva and cornea, starting in two minutes and lasting seven to ten minutes. If 5 per cent cocaine is instilled every three minutes for half an hour, the anesthesia generally extends also to the iris.

The *cocaine mydriasis* differs from atropine mydriasis: with atropine the dilatation is greater; the light reflex is preserved; the intra-ocular tension is always raised; exophthalmos is absent. The pupil does not react readily to pilocarpine or muscarine, while these constrict the cocaine pupil easily. These differences point to a different mode of action: Atropine paralyzes the oculomotor (constrictor) endings, while cocaine stimulates the sympathetic (dilator) mechanism; for when the sympathetic fibers have degenerated (eight days after extirpation of the superior cervical ganglion), ordinary doses of cocaine cease to be effective (Limbourg, 1892). Dilatation may still occur, however, with large doses or under special conditions. Simple (postganglionic) division of the sympathetic does not immediately abolish the cocaine reaction; the stimulation must therefore involve the endings; but since the dilatation is not as strong, it would seem that, ordinarily, the pupillo-dilator center is also concerned (Schultz, 1898). Under ordinary conditions the cocaine pupil continues to respond to oculomotor stimulation, showing that the constrictor mechanism is not paralyzed. Prolonged application of a 5 per cent solution, however, also paralyzes the oculomotor endings. Cocaine also inhibits isolated sphincter muscle (Yonkman, 1930). *Procaine* dilates the pupil, normal and denervated, from the blood stream (MacGregor, 1939). In *birds' eyes* cocaine produces no dilatation; in *frogs* this is marked.

Cycloplegia.—Strong solutions of cocaine act somewhat on the oculomotor endings, and therefore impair accommodation. This begins in five or ten minutes. The maximum is reached in thirty minutes and lasts ten to fifteen minutes; the normal is restored in one and one-quarter to two hours. The accommodation is merely disturbed by a drop of 6 per cent solution; high concentrations paralyze it completely. The mydriasis develops somewhat more slowly and is more lasting (Horovitz, 1912).

Intra-Ocular Pressure.—This may be unchanged, or raised or lowered (Tourriere, 1913). The reduction is probably due to the local vasoconstriction, which would tend to lessen the lymph flow into the chambers. This is partly counteracted by the mydriasis, which leads to obstruction of the lymph channels by the relaxed ciliary muscles (see "Atropine"). This obstruction may predominate and the pressure may thus be increased, especially in glaucoma (Myashita, 1913). Holocaine is said to have provoked acute glaucoma (Gjessing, 1915). Tropacocaine and acoine are probably inactive (Bollet and Curtil, 1911). The *retinal vessels* are strongly constricted by cocaine (Hirschfelder, 1915). This may be responsible for the occasional occurrence of optic atrophy (Harnack, 1912).

Catarrh, Hay Fever and Asthma.—Cocainization of the nasal mucous membrane may temporarily relieve attacks of hay fever and asthma. The astringent action renders it effective in acute coryza. The *danger of addiction* should preclude its use in these conditions; many cases were started by proprietary catarrh "cures." One per cent cocaine ointment has been recommended in *herpes zoster;* it is reported not only to relieve the pain, but to arrest the disease.

Urethra and Bladder.—The urethra is a good absorbing surface and has often given rise to poisoning. This danger is minimized by using dilute solutions. Even procaine is fairly effective. Metacaine, 1 to 4 per cent, is commonly used. With dog's urethra the hydrochlorides of alypin and tropacocaine are absorbed somewhat better than cocaine; apothesine, beta-eucaine and procaine are absorbed somewhat less efficiently; but the differences are not great. The rate of absorption increases with the dose and concentration. The absorption is more rapid during the first ten minutes, but continues quite markedly after this time. Alkalinization does not increase the absorption (Sollmann, 1918).

In *rectal surgery,* the action of local anesthetics can be greatly prolonged by applying them in oily solution (C. H. Morgan, 1935). Cocaine locally relieves *hemorrhoids,* producing contraction and diminishing pain. It has been taken by the stomach to prevent *vomiting* and dyspeptic pain. The addiction danger renders these uses inadvisable.

Dentine.—Dental enamel offers an effective barrier, and even with exposed dentine the anatomical arrangement of the tubules precludes sufficient penetration to produce effective local anesthesia. Apparent results are psychical. This holds also for the mixture devised by L. L. Hartman, 1936: thymol 1.5, alcohol 1 and ether 2 parts (Tainter, 1939).

Insoluble Anesthetics for Open Wounds and Ulcers.—The soluble anesthetics are absorbed too rapidly to be of material use in persistent pain. The limited and slow solubility of the free synthetic bases renders them more adapted to these conditions, but their practical usefulness is not great. They are employed for painful wounds, ulcers, etc., of the skin and accessible mucous membranes; for instance, after dental operations. Ethyl aminobenzoate (benzocaine, anesthesine) may be applied diluted with 5 to 20 parts of talcum or boric acid; or lozenges of 0.01 to 0.02 Gm. A 0.5 per cent emulsion of ethylaminobenzoate base in a synthetic resin-glycerin monostearate and water vehicle is more effective than a saturated solution in oil, and is especially useful for burns (R. Beutner, 1944).

Insoluble anesthetics have been used against the pain of gastric ulcer or cancer and other gastralgias, but their efficiency is doubtful. Anesthesine, cycloform, orthoform-new and propaesin are about equally effective through intact mucous membranes (Sollmann, 1919). They are practically nonirritant and nontoxic.

Conduction and infiltration anesthesia consists in the injection of the local anesthetic into or around the nerve trunk or in the area of its distribution, so as to block sensory impulses from the operative field. Since fatal effects may arise from the absorption of the anesthetic, the smallest amount of the least toxic agent that is effective should be employed, under conditions which minimize absorption. Procaine with the addition of epinephrine (1:100,000) is generally preferred. A well planned technic is important. It is not necessary to flood the entire field of operation, as in the earliest methods; nor even to infiltrate the whole line of incision, as in the "infiltration anesthesia" of Schleich (1892). It is now aimed to confine the anesthetic mainly to the nerves, by placing it where the nerves chiefly run, or injecting it into the nerves themselves (H. Braun).

Infiltration with oil solutions produces Wallerian degeneration of the nerve fibers, and therefore persistent paralysis. This was most marked with nupercaine, least with eucupine, procaine base being intermediate (D. Duncan, 1939).

Intravenous and intra-arterial anesthesia were introduced by Bier, 1908, and have a limited field, but are generally unsatisfactory and dangerous (Bevan, 1915). The action of cocaine is sufficiently selective so that a marked, though incomplete, general analgesia, without disturbance of consciousness or motor functions, can be produced by intravenous (Ritter, 1909; Harrison, 1911) or intra-arterial (Ransohoff, 1909) injection even without ligation.

Spastic Rigidity of Skeletal Muscles.—Local injection of 0.1 to 2 per cent procaine or other anesthetics blocks centripetal proprioceptive impulses and depresses the muscle, relaxing muscular tonus, normal and abnormal, such as spasmodic torticollis. It effects almost instantaneous relief of the pain, stiffness, malposition and incapacity of fibrositis, lumbago, acute sprains and fractures (Moynahan, 1939). The site of greatest tenderness may be infiltrated with 10 to 30 cc. of 1 or 2 per cent procaine hydrochloride (Outland and Hanlon, 1940). Even 1 or 2 cc. may give prompt, complete and often lasting relief in myalgia (M. Good, 1942).

Injected systemically, procaine relaxes traumatic tetanus (E. Meyer and Weiler, 1916 and 1917) and removes decerebrate rigidity, so that spontaneous movements of the limbs and of the respiration return. Its curare action may also be concerned in this effect. It relaxes Parkinsonian, but not myotonic rigidity (Allers and Hockstaedt, 1928; Liljestrand and Magnus, 1929). It has some systemic analgetic action (10 cc. of 2 per cent procaine hydrochloride), about comparable to that of acetylacetic acid, but not as lasting (Bigelow and Harrison, 1944, Wolff's method).—*Serum sickness* and *urticaria* are relieved by *intravenous injection* of procaine hydrochloride, 1 Gm. in 500 cc. of saline in the course of two hours. No untoward reactions were observed with this slow rate, but faster injection produces flushing, dizziness and generalized numbness (State and Wangensteen, 1946).

Spinal anesthesia is really nerve root anesthesia, produced by lumbar or sacral subdural injection of procaine or other local anesthetics, which anesthetizes the sensory nerve roots at their emergence from the spinal cord, and abolishes sensation in their entire peripheral distribution, beginning in two to ten minutes, and lasting half an hour to two hours. There is little if any interference with motor functions. Consciousness is, of course, preserved. The anesthesia extends to the level of the nerve roots reached by the anesthetic, the aim being to confine it to the lower half of the body. If it extends to the fourth ventricle, it paralyzes respiration. Other side actions consist in fall of blood pressure, in severe headache which may sometimes last for days or weeks; and in cord injury. Bronchial pneumonia and atelectasis are fairly common (Apgar, 1939). Spinal anesthesia may cause more psychic shock than does general anesthesia, but usually less somatic disturbance. It is *especially useful* in pulmonary disease, arteriosclerosis, bladder and rectal operations, impending uremia and in diabetic patients. It is more difficult and more dangerous for operations above the costal margin. If the respiration stops, artificial respiration is the most effective treatment (E. F. Hill and MacDonald, 1933). Strychnine and caffeine have little or no value. Epinephrine or ephedrine is injected if the blood pressure falls.

Historical.—Spinal anesthesia was demonstrated by Corning of New York in 1885 and introduced into practice by Bier, 1899, but it was then abandoned, and did not come into vogue until about 1904.

Technic.—The patient generally receives a preliminary sedative, morphine or barbiturate. The injection is performed by lumbar puncture, withdrawing some cerebrospinal fluid and injecting 3 to 5 per cent solution of procaine hydrochloride. The average dose is 1 mg. of drug per pound of body weight, the total not to exceed 200 mg. The slower the injection, the less the spreading. Increase of concentration produces longer anesthesia and greater relaxation, but more risk of damaging the nervous tissue. Ten per cent should not be exceeded. Pontocaine has been recommended for operations lasting longer than half an hour (F. W. Marvin, 1933). Epinephrine may be added; or ephedrine, 50 to 100 mg., may be injected intramuscularly, ten minutes in advance to counteract the fall of blood pressure. The spread of the anesthetic solution may be diminished by increasing its specific gravity by adding 5 per cent of dextrose, or its viscosity by 5 to 15 per cent of acacia (Smith and Porter, 1915). A special technic for spinal anesthesia of the chest was elaborated by Etherington-Wilson (Bourne, 1939).

Phenomena of Spinal Anesthesia.—These occur in the following order: loss of knee jerk; of plantar and cremasteric reflex; ascending analgesia; later, ascending loss of motor power. The upper limit is usually quite abrupt. Minor temporary motor paralysis occurs rather frequently if the dose is fairly large, not otherwise (J. L. Emmett 1934). Subjectively, there is an ascending feeling of warmth, swelling and heaviness. Occasional *toxic effects* are pallor, nausea, vomiting, sweating, feeble pulse, relaxation of sphincters, dyspnea. The most frequent *after-effects* are headache and insomnia. *Order of disappearance of sensation from the skin:* Baglioni and Pilotti, 1910, state this at first, of pain; then, after some time, cold; then, soon, heat. Finally, pressure. Recovery occurs in the reverse order. *To paralyze the anterior roots* would require a concentration about four times as high as suffices for the posterior roots (Sebastian). The *intestines* are firmly contracted and quiescent, probably from the morphine. Spinal anesthesia with procaine promptly abolished *paralytic ileus* produced experimentally in dogs by peritonitis or severe intra-abdominal trauma (Markowitz and Campbell, 1927).

Fall of blood pressure is a common phenomenon of spinal anesthesia (especially in patients with essential hypertension; R. Gregory *et al.*, 1943). Smith and Porter, 1915, found that it is due to paralysis of the splanchnic fibers in the cord, not in the medulla. Epinephrine with tropacocaine or procaine caused an even greater fall. Measures to restore the pressure were only temporarily successful. As the effects of the anesthetic began to wear off, sciatic stimulation produced a fall, instead of the normal rise. *The combined action of stovaine and strychnine* on the cord was investigated by Aron and Rothman, 1909; and Simon, 1915. The two drugs are not antagonistic; and strychnine does not render stovaine any safer.

The *spinal injury* depends on the nature, amount and concentration of the anesthetic agent. It is rather rare clinically when procaine is used in concentrations of less than 8 per cent. The nerves exposed to the greatest concentrations are most affected (M. J. Nicholson and Eversole, 1946). It is more common with some of the other anesthetics, *f. i.*, nupercaine. Higher concentrations of procaine in animals result in aseptic meningeal inflammation and degeneration of the myelin in the cord, with permanent paralysis (L. Davis *et al.*, 1931; Lundy *et al.*, 1933; Brock *et al.*, 1936, reviews the literature).

Injection of local anesthetics in the cisterna magna or local application to the fourth ventricle results in depression (chiefly in amplitude) and paralysis of the respiration, sharp fall of blood pressure and slowing of the heart, abolition of conjunctival and pupillary reflexes. The respiratory and vasomotor centers respond fairly well to stimulation by carbon dioxide; reflex stimulation is less effective. The animals can usually be saved by prompt artificial respiration (Hill and MacDonald, 1933; Nicholson and Sobin, 1936). Injection of ephedrine (2.3 mg. per Kg.) into the cisterna shortens the respiratory paralysis and hastens the return of the reflexes, much more effectively than intravenous injection. This may be useful in emergencies (Isenberger and Rice, 1936).

Caudal sacral anesthesia, injection below the termination of the spinal cord, blocks sensation from the urinary bladder, posterior urethra and uterus. *Continuous caudal analgesia,* by repeated injections of the local anesthetic, is used in obstetrics. It abolishes pain without interfering with the uterine movements. It relaxes the cervix, which is kept contracted by parasympathetic impulses through the second, third and fourth sacral nerves (R. A. Hingson, 1944). Spinal anesthesia heightens the response of the pregnant uterus to mechanical stimulation (P. Malpas, 1944).—*Intravenous injection* has also been tried successfully in obstetrics to dull the pain of the second stage of labor, presumably by central action (F. M. Allen, 1945).

Sympathetic Stimulation.—The phenomena of systemic cocaine poisoning are largely those of sympathetic stimulation, but not so consistently as with epinephrine (D. F. MacGregor, 1939). The sympathetic stimulation is mainly central (midbrain), but partly peripheral. The chief manifestations of sympathetic stimulation are (1) sensitization to epinephrine, but antagonism to ephedrine by peripheral action; (2) mydriasis and slight exophthalmos by central and peripheral action; (3) cardiac acceleration (chiefly central). Other sympathetic symptoms are: constriction of the blood vessels, erection of hair and relaxation of the intestines. High concentrations of cocaine paralyze all smooth muscle. *Procaine* also produces sympathetic stimulation on systemic administration, dilating the pupils, augmenting the heart, inhibiting the intestines, increasing the pressor action of tyramine (D. F. MacGregor, 1939). It inhibits the response to stimulation of sympathetic nerves, but not epinephrine. It combats the actions of *acetylcholine* on the heart, lungs and intestines (R. Hazard, 1946).

K. V. Thimann, 1943, suggested that the local anesthesia is due to *competition with acetylcholine* for the excitable substrate.

The cocaine sensitization to epinephrine is manifested especially in the blood pressure rise, but can be demonstrated also in the bronchial dilatation and in the uterine actions. It is not shared by the synthetic cocaine substitutes, not even by dextro-pseudococaine (Mercier, 1931). The sympathetic effects are produced in rabbits by the hypodermic injection of 35 to 50 mg. of cocaine; or by 10 mg. of cocaine with 1 mg. of epinephrine (Mills, 1919)

Sympathetic Ganglia.—Cocaine and procaine abolish the response to stimulation of their preganglionic fibers, to acetylcholine and to nicotine, and suppress their normal output of acetylcholine during stimulation (D. F. MacGregor, 1939; A. M. Harvey, 1939).

Circulation.—The effects of cocaine on the general circulation are partly central, partly peripheral. They vary according to the dose, and are also influenced by individual susceptibility.

Very small doses diminish the pulse rate, by stimulation of the vagus center (Vulpian, 1884). There is a quick rise of *blood pressure* from stimulation of the vasomotor center; this is followed by a temporary fall due to the slowing. *Moderate doses quicken the pulse,* mainly by central and peripheral depression of the vagus (v. Anrep, 1880) with some stimulation of the accelerator center (Mosso, 1887). *The pressure rises* (v. Anrep) from stimulation of the vasomotor center (Berthold, 1885), aided by the faster heart rate. The vasomotor factor is predominant, for the rise is practically absent if the cord is cut. *Large doses cause severe fall of pressure* and slow and weak pulse (v. Anrep), from the depression of the medullary centers (collapse) and of the cardiac muscle.

Cocäine stimulates the cardio-inhibitory center when *perfused through the medulla* of the turtle (Bush, 1920). In *perfused mammalian heart* low concentrations slow and strengthen the contractions; higher concentrations cause slowing and weakening; fatal concentrations give diastolic arrest (Kochmann and Daels, 1908; and Prus, 1913). Kuroda, 1915, observed no stimulation in excised hearts of mammals or frogs. MacGregor, 1939, reports amplification of the contractions of isolated auricle of cats' hearts by *procaine.*

The Frog Heart.—Dilutions of cocaine 1:500,000 increase the excursions of Straub hearts; 1:300,000 slow and diminish the systole; 1:60,000 arrest the ventricle (Kochmann, 1921). Perfusion produces heart block, which may be prevented by atropine or epinephrine (Kuroda, 1915). Direct application of 6 per cent cocaine to the sinus suppresses the nodal rhythm and therefore arrests the heart, while the same application to the auricles or ventricles does not produce arrest (Maestrini, 1916). *The turtle heart* is also stimulated by low and depressed by somewhat higher concentrations (H. G. Bayer, 1885). *Procaine* depresses similarly to cocaine (Roth, 1917). Local application of procaine to the sinus or auricles of the frog heart renders them irresponsive to electric stimulation, when they still beat spontaneously and set the pace for the ventricle (H. Witz, 1938).

Intrapericardial injection of local anesthetics (2 cc. of 5 per cent procaine in dogs) abolishes completely the inhibitive response of the heart to vagus stimulation. *Direct application to the epicardium* (1 cc. of 10 per cent cocaine, mesycaine, procaine or potassium chloride) raises the minimal strength of stimulus required to provoke extrasystoles, and immediately arrests tachycardia or auricular fibrillation from operative manipulation of the heart (Mautz, 1936; R. F. Baker and Madden, 1944). *Intravenous injection* of procaine (10 to 20 mg. per Kg.) or of pontocaine into dogs also prevents *auricular fibrillation* from faradic stimulation or local application of acetylcholine to the heart (Hirschfelder and Tanuales, 1942). Intravenous injection also prevents *ventricular fibrillation* and the production of heterotopic rhythms by electric stimulation, epinephrine (especially during cyclopropane anesthesia; Burstein and Marangoni, 1940) or barium, although 7.5 mg. per Kg. has no direct effect on conduction time or refractory period (Van Dongen, 1938; Mautz, 1937). This method of arresting ventricular fibrillation is effective in resuscitation as a preliminary to establishing normal rhythm by direct electric stimulation of the heart (C. S. Beck and Mautz, 1938). Para-aminobenzoates also protect somewhat against epinephrine-cyclopropane ventricular fibrillation in dogs, but much less effectively than procaine (Marangoni *et al.,* 1940).

The blood pressure reacts similarly to cocaine and procaine, being raised by small and lowered by large doses (Roth, 1917). Even small concentrations of cocaine potentiate the *epinephrine constriction* (Braun, 1914; Fischel, 1915). Cocaine therefore increases the pressor effect of epinephrine. This may result in a marked rise of blood pressure when cocaine is used clinically in connection with epinephrine; and the excessive vasoconstriction may be the factor in the toxicity (E. L. Ross, 1922). The *carotid sinus blood pressure reflex* is abolished by cocaine (10 mg. per Kg.) and by large doses of procaine; also in spinal anesthesia by procaine or percaine (Heymans *et al.,* 1933). *Traumatic shock* from crushing of muscles is prevented or mitigated by local or spinal anesthesia (G. W. Crile and Lower, 1914; Eversole *et al.,* 1944). The *cerebral circulation* is increased by cocaine and still more by procaine (Frankfurther and Hirschfeld, 1910). The vessels of the retina and pia mater are constricted (Hirschfelder, 1915). The **urine flow** is usually diminished, but sometimes increased, depending mainly on the vasomotor effect.

Smooth muscle is generally first stimulated, then depressed by cocaine, regardless of innervation. The stimulation is therefore not through the sympathetic; nor is it parasympathetic, for it is not prevented by atropine. It must be exerted directly on the muscle. This applies also to the synthetic cocaine substitutes (Waddell, 1917). The reactions of the *uterus* to cocaine appear confusing: G. H. Miller, 1926, reported that a dilution of 1:10,000 acts like epinephrine 1:1,000,000, *i. e.,* augmentor and depressor depending on the animal and state of pregnancy; but Thienes, 1928, found that half the uteri responded inversely to the two agents. *Excised ureter* is stimulated by cocaine and by procaine (Roth, 1917). The *urinary bladder* (excised) is stimulated by cocaine, less by the synthetic substitutes. Mixtures of these give simple summation. So do pituitary and epinephrine, the latter being depressant (Waddell, 1917). Karashima, 1927, confirmed the stimulation by small doses of cocaine. *Excised bronchial muscle* is somewhat dilated (Trendelenburg, 1912). The bronchiolar constriction of morphine is completely abolished by hypertonic injection of cocaine (10 mg. per Kg.); that of histamine only incompletely; that of physostigmine and pilocarpine is not abolished (Swanson) *Excised small intestine* responds to dilute solution of cocaine by either stimulation or depression (Roth, 1917; Thienes, 1928; Karashima, 1927) or by inhibition followed by marked rise of tonus (G. H. Miller, 1926). Concentrations above 1:2000 are usually depressant. The pH of the Locke's solution has marked effects on the response of the cat's intestine (Salant and Parkins, 1932). In *unanesthetized dogs* with Thiry-Vella fistulas, intravenous injection of cocaine also causes variable responses, the tonus being sometimes increased, sometimes lowered

(Gruber, 1936). The *esophagus, stomach* and *colon* are stimulated to increased tonus and contractions by dilute solutions of cocaine; concentrations above 1:20,000 tend to depress (Thienes, 1928).

Striated Muscle.—Cocaine and procaine weaken neuromuscular transmission in mammals and frogs, so that the muscle responds better to direct than to nerve stimulation. They reduce the response toward tetanic stimuli to a single twitch, and weaken acetylcholine and potassium contracture. These effects resemble those of curare, but occur also after degeneration of the nerve (D. F. MacGregor, 1939; A. M. Harvey, 1939). Neostigmine contractions are depressed by procaine and cocaine much more readily than normal contractions, so that the action has been attributed to diminished production of acetylcholine at the neuromuscular junction (Jaco and Wood, 1944). Procaine also depresses and abolishes the response of the muscle to direct stimulation, the effect being nearly as great as that on the nerve (Sollmann). All local anesthetics, even in very dilute solutions, counteract various *spasms*, such as those of nicotine, guanidine and veratrine, also after curarization or after degeneration of the nerve endings. The antagonism is mutual (Frank and Katz, 1921). Procaine (1:500) prevents *caffeine contracture and rigor* and the overproduction of lactic acid, even in concentrations which do not directly depress the response of the muscle to stimulation. The concentration, however, must increase with that of the caffeine. The action is reversible, *i. e.*, when the procaine is washed away, the muscle again becomes susceptible to the caffeine. Established rigor is not removed. Cocaine acts similarly, but requires considerably higher concentrations; anesthesine is quite effective; atropine lacks this action (Schüller, 1925).

Glandular secretions are but little affected by cocaine. The *saliva* flow is not stimulated (Kuroda, 1915). The albumin and shell material in the *oviduct secretions* of birds appear to be somewhat decreased (Riddle and King, 1921).

The **central actions of cocaine** are rather variable and complex, depending largely on the dose.

Cerebral Stimulation.—The first systemic effect of cocaine is psychical stimulation, somewhat resembling that of caffeine. This differs considerably in degree and in kind with individuals, and may be manifested as alertness, loquacity, elation, wakefulness, excitement, sometimes markedly sexual; or anxiety and flutter. The stimulation is greatest in excitable individuals and may interfere seriously with operations. Patients should be forewarned of the anxiety complex.

Oral administration of 1 to 3.5 mg. per Kg. of body weight to nonhabituated subjects results in slight rise of temperature (larger with larger doses); slight increase of spinal reflexes; no important changes in pulse, blood pressure and respiration; slight alterations of mental activity in some cases (V. Z. Ortiz, 1944).

The natives of the Andes chewed coca leaves to *suppress hunger and fatigue*, and cocaine is reported to counteract mountain sickness. The increased resistance to fatigue has been confirmed by "blind" experiments with the ergograph (0.05 to 0.1 Gm. of cocaine by mouth; Thiel and Messig, 1930). O. Boje, 1939, reports that cocaine is the only agent that produces definite improvement of athletic performance; caffeine was not effective. In dogs, 4 mg. of cocaine per Kg. hypodermically increase resistance to swimming fatigue by 70 to 150 per cent; caffeine (10 mg. per Kg.) by 37 to 108 per cent; metrazol (5 mg. per Kg.) did not increase resistance (Gutierrez-Noriega, 1944).

Animals respond to cocaine by great *restlessness*, sometimes by circus movements. The suppression of the continuous motor activity induced by cocaine in mice may serve as a means of assaying the potency of sedatives (Modrakowski and Rusiecki, 1937). Cocaine increases the resistance to general anesthesia. Mosso, 1887, and Airila, 1913, found that 10 to 40 mg. of cocaine, hypodermically, waken dogs or rabbits from deep chloral sleep. Most of the synthetic local anesthetics are *analeptic* to morphinized rabbits, but less so than cocaine, and the effective dosage is near that which convulses (Keil and Gropp, 1934).

Incoordination, Narcosis, Convulsions.—The stage of stimulation may be short or even absent. With somewhat larger doses it is usually succeeded by depression, first of the coordinating functions. The movements lose their purposive type and become choreic. General narcosis follows and then epileptiform convulsions, located chiefly in the midbrain. If the paralysis is rapid, the convulsive stage may not appear.

The site of the convulsant action appears to be complex. After removal of the hemispheres, cats respond to cocaine by a short period of motor excitement, followed by strong tonic contractions of the extensors. The differences from the ordinary epileptiform convulsions are probably indirect (modification of inhibitions, etc.) After section of the posterior roots, cocaine produces extensor spasms, apparently by acting above the cord and below the corpora quadrigemina, perhaps on the pontine nucleus (Allers and Hochstaedt, 1928 and 1930). Feinberg and Blumenthal, 1887, reported that cocaine convulsions do not occur in dogs after ablation of the cerebral cortex, or in newborn animals in which the cortical motor centers are not yet excitable. Rabbits deprived of the hemispheres do not show the clonic convulsions or respiratory effects; but they do exhibit tonic convulsions and "running movements." Their resistance to toxic doses is increased (Morita, 1915). *The action currents of cerebral cortex* show attacks of rapid potential variations, succeeded by temporary unexcitability as with other convulsants, such as caffeine and strychnine (Fischer, 1932). The ganglion cells of the cerebral cortex reveal *histologic changes*, primarily in the basophilic granules of the nuclei (Fukunaga, 1926). *Frogs* show increase of voluntary movements and exaggeration of reflexes, sometimes leading to convulsions. This is followed by paralysis of the whole central nervous system. In frogs from which the brain has been removed, cocaine causes at first an increase of the reflexes, then convulsions, and finally total paralysis.

In intact animals this effect is obscured by the action on the higher centers of the nervous system.

The **respiration** is at first accelerated. During the spasms it is irregular. The volume then diminishes. It may assume the Cheyne-Stokes type. Respiratory paralysis is the usual *cause of death*. This is also the first center to fail when the cocaine is applied locally to the fourth ventricle. Roth, 1917, found that small doses of procaine also increased the respiration, large doses being depressant.

Emesis.—The frequent vomiting in cocaine poisoning is perhaps due to the medullary stimulation, but its mechanism has not been fully investigated.

Temperature.—*Cocaine* produces hyperpyrexia in mammals, due to increased heat production, by the motor excitement and rise of basal metabolic rate, reinforced by the convulsions. It probably acts directly on the midbrain temperature centers. Cocaine lowers the temperature of birds (L. Forchheimer, 1931; the paper also discusses the relative susceptibility of birds to other poisons). *Procaine* lowers the temperature of mammals by increasing heat loss. It is antagonized by thyroxin and by dinitrophenol (Alwell *et al.*, 1937).

Metabolism.—In man, 0.1 Gm. of cocaine hydrochloried by mouth increases the basal metabolic rate by 7 to 22 per cent in twenty-five to thirty minutes, returning to normal in fifty minutes. There is also rise of temperature, respiration rate and blood pressure (R. Herbst and Schellenberg, 1931). In *rabbits*, large doses of cocaine cause rapid loss of weight. The quantity of urine, its specific gravity and particularly the urea, are diminished, while the incompletely oxidized (extractive) nitrogen is increased (Maestro, 1904). The effects of *repeated injection on dogs* have been investigated by Underhill and Black, 1912: doses of 10 mg. (per kilogram) produced no change in fat or nitrogen metabolism; 15 mg. gave a slight impairment of fat utilization, and considerable decrease of body weight; 20 mg. markedly decreased the nitrogen and fat utilization. The nitrogen balance may become negative. Lactic acid excretion was markedly increased in well fed dogs, but not in starvation—the increase being probably due to the muscular activity. The *blood sugar level* is not changed (cats, 15 to 35 mg. per kilogram), except as a result of excitement (Schaer, 1915).

Acute poisoning by local anesthetics is fairly frequent, especially with cocaine, and is likely to be fatal. Reliable statistics of fatalities are not available, but they are more common than is ordinarily supposed (E. Mayer *et al.*, 1920–1924). A large proportion of the accidents (25 per cent in one series) are due to mistakes in the drugs, concentration and dosage. Susceptibility varies greatly, owing to differences of absorption and of destruction, and to varying response to the actions. Fright plays a considerable part.

Safe and Toxic Dosage of Local Anesthetics.—Probably all commonly used local anesthetics have produced fatal accidents. These depend not only upon the absolute dose, but also on the rate of absorption, on idiosyncrasy and on other conditions. The Local Anesthetic Committee of the American Medical Association made recommendations (E. Mayer, 1924), which should minimize the accidents. The following are the most important: Procaine appears the safest of the more widely used local anesthetics and may be employed for subcutaneous and submucosal injections; but the concentration should not exceed 1 per cent. Cocaine and butyn should not be injected under the skin or mucous membranes, but restricted to surface application. The total quantity of cocaine should not exceed 0.06 to 0.1 Gm. (1 to 1½ grains). The patient should be recumbent, if the operation permits. With nervous patients, it is advisable to inject morphine fifteen minutes before the local anesthetic, and to delay the start of the operation till twenty minutes after the injection of the local anesthetic (Mayer *et al.*, 1920). Urethral injections are especially dangerous, and should be avoided if there is trauma or stricture.

Strict attention should be given to prevent the confusion of procaine and cocaine. The solutions should be kept in different kinds of bottles. Cocaine solution may be distinguished by tinting with sodium fluorescein, 1 mg. per Gm. of cocaine. This would also show the concentration of the solution.

The ordinary fatal dose of cocaine is considered to be about 1.2 Gm. (Watson-Williams, 1924), but death has been reported from 20 mg., and serious poisoning from 2 drops of a 4 per cent solution (5 mg.) on the conjunctiva, and with three drops of ½ per cent cocaine (1 mg.) in a tonsil operation (Mayer). In other cases, very large doses produced no effect (bibliography, Roth, 1917). *Dilution* slows the absorption of cocaine and insures its thorough utilization, and thus economizes its use. Solutions above 1 per cent should not be used for hypodermic injection. With solutions of ½ per cent and proper precaution, Reclus considers 0.2 Gm. quite safe. The addition of *epinephrine* to injections reduces the toxicity materially, chiefly by delaying absorption (Zaus and Moody, 1936; Beutner *et al.*, 1936). All local anesthetics are less toxic when injected into an *artery* than by vein (Kuroda, 1927), presumably because they reach the general circulation more gradually.

Safe Operations.—In open wounds, body cavities or other surfaces from which any excess will be moved when the operation is completed, the total quantity of cocaine is practically immaterial if dilute solutions (0.1 to 0.2 per cent) are employed, for only a small fraction will be actually absorbed.

Dangerous Operations.—Cocaine is especially dangerous when 2 to 10 per cent solutions are injected into closed mucous or serous cavities, such as the urethra, bladder, scrotal sac, etc. Very severe poisoning has repeatedly followed after urethral injection of 1 Gm. in 5 to 20 per cent solution, in one case even after 7 cc. of 1 per cent (70 mg.). Indeed, a fairly large number of toxic cases are reported from 10 to 50 mg. in 5 to 20 per cent solution (Weigand; H. Braun, 1914). Tonsil operations, when cocaine is injected, show many more fatalities than do operations on the nose (Mayer). The toxicity is increased by severe hemorrhage, also by chloral narcosis; probably by interference with the activity of the liver (Eggleston and Hatcher). Procaine proved fatal in a tonsil operation with 4 cc. of ¾ per cent, injected with epinephrine (Mayer).

The **toxic symptoms** are similar for cocaine and the synthetic substitutes, procaine, apothesine, butyn, etc. (Mayer, 1924). Fatal cases run a rapid course, with anxiety, sudden fainting, extreme pallor, dyspnea, sometimes brief convulsions, arrest of respiration and death generally in a few minutes. With smaller doses or slower absorption there is confusion, laughter, loquacity, vertigo, motor excitement; quickened pulse and palpitation; irregular respiration. Larger doses cause pallor; chill, with sweat and rise of internal temperature; dilated pupils and exophthalmos; nausea, vomiting and abdominal pain; great anxiety; disturbance of cutaneous sensation (worms under skin; etc.), feeling as if limbs had disappeared; finally delirium, dyspnea and Cheyne-Stokes respiration, extreme pallor of face, widely dilated pupils, strong tremors which progress to clonic convulsions, unconsciousness, rise of temperature and death by collapse and asphyxia. If death has not occurred within a few minutes, the patient will almost always recover. Unconsciousness and Cheyne-Stokes respiration may persist for one or two hours. Recovery may be followed by more lasting apprehension, insomnia, psychic depression and melancholia.

Symptoms in animals are similar to the clinical. *Intravenous injection of fatal doses into cats* produces almost instant extensor spasm, fixation of the respiration and sudden cessation of the heart. *Sublethal intravenous injections* cause immediate stimulation of the respiration and abrupt fall of blood pressure of cardiac origin; the heart rate is inconstant, but generally slowed. The respiration may be temporarily arrested. Within a minute, the heart begins to improve and the blood pressure rises; the respiratory stimulation diminishes; there may be brief but severe clonic convulsions. Within five minutes the animals may be apparently normal. As the doses approach the fatal, the convulsions are more prolonged, and recovery is slower, especially after cocaine (Eggleston and Hatcher, 1919).

The **treatment of poisoning by local anesthetics** should begin with prevention, the selection, dosage and technic of the administration. Previous administration of a sedative, especially of the barbituric series, diminishes the risk, by suppressing the convulsions and their interference with respiration, so that animals survive one and a half to four times the ordinary fatal dose of cocaine or procaine, if administered hypodermically (Tatum and Collins, 1926; Knoefel, Herwick and Loevenhart, 1930). Clinically, 0.2 Gm. of phenobarbital or 0.6 Gm. of sodium barbital may be administered an hour before operation (M. R. Guttmann, 1928; E. Y. Martin, 1928). Barbiturates do not prevent the direct circulatory collapse and depression of respiration which occur on intravenous injection of procaine (Isenberger, 1930), and are useless or harmful either for prophylaxis or treatment if the anesthetic agent is rapidly absorbed; but if the symptoms develop slowly, the suppression of the convulsions is at least helpful (Malone, 1934; Beutner *et al.*, 1936).

Knoefel *et al.*, 1930, reported the order of the antidotal efficiency of hypnotics as: amytal (highest), phenobarbital > barbital > paraldehyde > chloral > urethane and ether. A. M. Hunt, 1938, found evipal effective in controlling procaine convulsions that had lasted half an hour. Intracisternal injection of ephedrine is effective against the procaine respiratory paralysis (Isenberger and Rice, 1936).

If an overdose of the local anesthetic has been taken by mouth, evacuation and chemical antidotes are indicated; if the anesthetic was injected, absorption should be checked by ligation, if possible; for whatever delays death is likely to save the life in view of the rapid destruction of these drugs. If the symptoms have developed, the head should be lowered, the convulsions arrested by intravenous injection of sodium pentobarbital or amytal, and artificial respiration instituted if necessary, with cardiac massage if the circulation fails. The use of epinephrine or morphine is not advised (Emil Mayer, Commission, 1924).

Epinephrine, when 1:50,000 is added to injections of cocaine or procaine, is reported to increase the toxicity for mice materially; below 1:85,000 it had little effect (Gurd and Sachs, 1939). *Ephedrine,* 1:1000, diminished the toxicity and increased it only above 1:200 (J. D. P. Graham and Gurd, 1940). Failing respiration is not improved by metrazol, caffeine, lobeline or amphetamine. Artificial respiration is generally successful in saving dogs from the M.L.D., 14.6 mg. of procaine per Kg. with fast intravenous injection (J. R. Schamp, 1941).

L. Butturini, 1934, reported that *intravenous injection of dextrose* mitigates cocaine convulsions and raises the M.L.D. It had no effect on the toxicity of strychnine, santonin or calcium chloride. *Calcium chloride* injection was reported ineffective by Soma Weiss, 1923, but Beutner and Miley, 1938, claim that it protects against procaine convulsions. Beutner, 1940, attributes this to diminished absorption. Mersalyl, mercuric chloride and lead nitrate when mixed with procaine delay its absorption by precipitation (V. G. Haury, 1941). *Magnesium* injection is harmful (Knoefel, Herwick and Loevenhart, 1930). *Pituitary* solution has been recommended (Nielson and Higgins, 1923).

Fate of Cocaine.—This is partly destroyed in the organism, but mainly excreted unchanged in the urine.

McIntyre, 1936, reported the recovery of 429 mg. of cocaine from the urine of a patient who survived for twelve hours with barbiturate treatment after the peritonsillar injection of 800 mg. of cocaine. Tatum and Seevers, 1929, reported that dogs excrete cocaine by the urine, but that rabbits do not. Langecker and Lewit, 1938, found that rabbits detoxicate cocaine better than do guinea pigs or cats; percaine was poorly detoxicated by all three; atropine equally well by rabbits and guinea pigs. Cocaine is detoxicated in rabbits by rapid demethylation, atropine by ester hydrolysis. Procaine, apothesine and stovaine and probably the other synthetic anesthetics are rapidly destroyed in the liver.

Persistence of Effect and Cumulative Action.—Most synthetic local anesthetics are destroyed so rapidly in the body that the toxicity is much smaller when the drug is introduced slowly. Cocaine and phenocaine (holocaine), however, are not destroyed nearly as promptly (Eggleston and Hatcher, 1919).

Procaine is destroyed (hydrolyzed) by the blood, inside as well as outside the body, in some twenty minutes with physiological doses. This is due to an esterase which is formed in the liver and is therefore absent in hepatic disease (R. Hazard, 1946).

Destruction of Cocaine in Vitro; Sterilization.—Long-continued boiling decomposes cocaine into benzoyl-ecgonine and methyl alcohol. It was therefore believed that solutions could not be sterilized by boiling. In fact, however, the decomposition, on boiling half an hour, is insignificant; longer boiling only decreases the activity, for the decomposition products are merely inactive and not toxic. Any decomposition on boiling is probably due to alkalinity from the glass (Baumeister, 1917).

Watery solutions of basic cocaine deteriorate rapidly, losing their anesthetic power within seven hours, and still more rapidly when heated. Basic procaine and alypin are stable in solution (Gros, 1912). *Solutions of cocaine salts* are much more stable than basic solutions, but liable to mold.

Procaine solutions are said to be difficult to sterilize (Ersner, 1917). They turn brown on keeping, but their efficiency or toxicity is not altered, at least for several months. Solutions that have developed a sediment (generally molds) should not be used (Bonar, 1923).

Resistance to Putrefaction.—Positive tests for cocaine were obtained in cadavers even months after death (Palet, 1919).

Benzoyl ecgonine was found by Stockman, 1886, to resemble caffeine in its central and muscular action. It had no effect on sensory nerves or the pupil.

Cocaine Addiction.—The elation and euphoria which cocaine induces in susceptible individuals tend to render it a "habit drug"; but it is more likely to be used for occasional "jags" by Negroes, prostitutes and criminals, rather than daily, as is morphine. The treatment is therefore easier and more likely to be successful. It may be used continuously, however, as by the South American natives. Addiction occurs most rapidly with intravenous, then with hypodermic, least with oral administration. The M.L.D. is only twice as high as the optimal stimulating dose (Gutierrez-Noriega and Ortiz, 1944). Cocaine inebriation is active and sociable, in contrast to the dreamy state induced by morphine. It may induce a more or less maniacal condition, in which the individual becomes dangerous to others. The *immediate effects* include the phenomena of sympathetic stimulation, resembling hyperthyroidism: tachycardia, polypnea, mydriasis and exophthalmos, fine tremors. Some individuals, especially women, react with marked erotic excitement. The stimulation is succeeded by depression tremors, pallor, sunken and unsteady eyes (Owens, 1912). The *chronic effects* show rapid emaciation and severe psychic disturbances, insomnia, hallucinations, apathy, melancholia, suicidal mania (Vallon and Bessiere, 1914). The pupils are inconstant. Acne is common. It is claimed that considerable *tolerance* is acquired, so that the daily hypodermic consumption may reach 2.5 Gm., or even 10 Gm. (Grode, 1912). Chouppe, 1889, reported that morphinists are relatively tolerant to cocaine. Sudden withdrawal leads to abstinence symptoms similar to those of morphine. *With cocaine snuffing,* where smaller amounts are used in intermittent debauches, the chronic effects, the craving and the abstinence symptoms are proportionately less marked. Such patients develop atrophic rhinitis, with characteristic ulceration of the nasal fossae (Owens; also present in heroin snuffing, Phillips). The *treatment of cocaine habit* coincides with that of morphine addiction. The prescribing of cocaine and tropacocaine comes under the Harrison Antinarcotic Law. This does not apply to the synthetic substitutes.

The effects on habituated subjects (South American Indians) are identical for cocaine (4 mg. per Kg. by mouth) and for chewing the leaves (generally about 100 Gm.). The most frequent phenomena are anesthesia of the mouth, slight mydriasis, moderate tachycardia, rise of blood pressure and of temperature, increased metabolic rate, intensification of reflexes, some modification of mental activity, nervousness, euphoria and insomnia (F. R. Mendizabal, 1944). Beginners may have nausea. The commonest mental symptoms are minor alterations of visual and auditory perceptions, illusions and pseudohallucinations (rarely true hallucinations), thought disorders and delusions, turning from reality to a dream world. *Abstinence symptoms* are light and brief (Gutierrez-Noriega, 1944).

Cocaine Habituation in Animals.—Continued administration to dogs and monkeys induces psychoses similar to the human, and marked desire for the drug (Tatum and Seevers, 1923), but withdrawal does not cause serious reaction or erethismus (Grode, 1913; Tatum and Seevers; Downs and Eddy). Animals do not acquire tolerance; on the contrary, the toxic, convulsant and excitant effects of a uniform dosage increase for several weeks and then remain level (Gutierrez-Noriega and Ortiz, 1944). The M.L.D. for rats falls progressively. Dogs habituated to cocaine are hypersensitive to ephedrine, and tolerant to morphine (Downs and Eddy, 1932; Stanton, 1938). Animals that have recovered from toxic doses show diminished resistance to lethal doses; this is probably due to toxic injury of the tissues, liver and other, that normally destroy the cocaine (Atkinson and Tatum, 1925). The *liver* of mice subjected to increasing doses of cocaine shows vacuolar degeneration and often extensive fatty infiltration, with increase of neutral fat especially of cholesterol, the phospholipids remaining constant (P. L. MacLachlan and Hodge, 1939).

Cocaine on Body Weight and Growth.—No effects were produced in rats by doses corresponding to 2½ grains of cocaine per man per day, administered continuously for eight months. Procaine and other synthetic anesthetics reduced the weight, after a few weeks, with doses corresponding to 5 grains per day (Sollmann, 1924).

Comparison of Cocaine and Its Substitutes.—Cocaine is satisfactory from the standpoint of efficiency, penetration, and practical absence of tissue injury. However, its rather high toxicity has led to the use of substitutes wherever practical. Some of these present advantages in special fields, although they lack the general applicability of cocaine.

The differences between cocaine and its substitutes concern especially the following points:

Toxicity.—It is generally believed that cocaine has the highest toxicity. This conclusion was based primarily on animal experiments, but seems in harmony with clinical experience.

Toxicity Comparisons on Animals.—Extensive series of experiments have been published, for instance by Kochman, 1914. These show that cocaine is perhaps three times more toxic to guinea pigs, on hypodermic injection, than are most of the substitutes. It may be questioned whether this reproduces the absorption and destruction sufficiently to justify transfer to clinical conditions.

Intravenous Toxicity for Cats.—This would be a more definite index of absolute toxicity, but its clinical application would also be limited. Eggleston and Hatcher, 1918 and 1919, found the M.L.D. (mg. per Kg.) as follows: Alypin holocaine, 10; Beta-eucaine, 12.5; Cocaine, 15; Apothesine, 20; Tropacocaine, 20–25; Stovaine, 25–30; Nirvanine, 30–35; Procaine, 40–45.

Combinations of any two of these local anesthetics produce simple summation of the effects, so that they would not offer any advantages from this standpoint. The systemic actions of all are similar, death occurring by combined cardiac and respiratory paralysis. The *hypodermic fatal doses* are therefore more than five times greater than the intravenous, except with the relatively indestructible cocaine and phenacaine.

Irritation and Tissue Injury.—In ordinary concentrations, cocaine, procaine and apothesine are practically nonirritant. Eucaine, alypin, phenacaine (holocaine), and benzyl alcohol produce smarting and some pain, but no permanent injury. Tropacocaine raises wheals on the scarified skin. Stovaine and quinine-urea cause more pain and lead to induration or gangrene if the ordinary concentrations are exceeded.

The irritative phenomena have been compared for the intracutaneous injection by Braun, 1905. Procaine up to 5 per cent produced no pain or hyperemia. Stovaine caused strong local irritation, even with dilute solutions, and gangrene with 5 to 10 per cent. Alypin as dilute as 0.1 per cent gave pain and hyperemia, but less than stovaine; 1 per cent produced persistent irritation; and 5 per cent, gangrene. Cocaine is practically nonirritant. The irritation has also been studied by Le Borcq, 1919, Kochmann, 1914, and Closson, 1914.

Stability of Solutions.—Cocaine solutions should be freshly made, although their deterioration is not so rapid as was formerly supposed. Alypin solutions also should not be kept longer than a week (Impens, 1905). The others keep for a considerable time. Phenacaine (holocaine) solutions must be slightly acid and are therefore irritant. Procaine solutions become discolored. Solutions of the synthetic local anesthetics may be *sterilized* by boiling, and cocaine solutions can safely be boiled for a few minutes. The *solubility of the bases in oil* is, in descending order, alypin (all proportions), eucaine, procaine, cocaine (Gros, 1910).

Addiction has not been reported for the cocaine substitutes.

Structure of Cocaine.—Cocaine is the methyl-benzoyl ester of ecgonine, a base closely related to tropine, the corresponding base of atropine, both being pyrrolidine derivatives. *Ecgonine* itself produces only the least important of the actions of cocaine, *viz.*, the hepatic degeneration. The other actions are developed only by the entrance of *both* radicals. The methyl may be replaced by any other alkyl radical, without changing the actions of cocaine. The benzoyl radical, however, can not be replaced by other aromatic acids (possibly with a few exceptions), nor by fatty acids without great impairment of the local anesthetic action. Indeed, the presence of the benzoyl group gives the anesthetic properties to other alkaloids. It is present in most cocaine substitutes. *Relations of chemical structure and action* have been studied for an extensive series of local anesthetics by Gilman, Goodman *et al.*, 1942.

PREPARATIONS: (In Alphabetic Sequence):—**Allocaine S** is a complex benzol derivative. Kubota, 1919, claims that it is somewhat less toxic and more anesthetic than procaine, but rather more irritant. It does not appear to have any real advantage.

Alypin Hydrochloride, N.N.R. (Amydricaine Hydrochloride), Benzoxy-dimethylamino-methyldimethyl-aminobutane hydrochloride; it is efficient on mucous membranes, and is used especially in the urethra. In structure it resembles stovaine. It is used in about the same concentrations as cocaine, but is more irritant. Several cases of sudden collapse and asphyxia, after its injection, have been reported (Ritter, 1912; Lichtenstein, 1914). The maximal dose of 0.25 Gm. must not be exceeded. Alypin solutions should not be kept longer than a week (Impens, 1905). They are not readily precipitated by alkalis, and the base is very soluble in oils.

Apothesine Hydrochloride, N.N.R., Diethyl-aminopropyl cinnamate hydrochloride, in properties and uses resembles procaine. Dosage, for injection anesthesia, 0.5 to 2 per cent, with epinephrine 1:100,000. On cornea, 2 to 4 per cent. Spinal anesthesia, 2 cc. of 4 per cent. Apothesine is relatively safe; but severe collapse has been reported from the injection of 1 and 2 per cent solutions in throat work (Mayer *et al.*, 1920), and death has occurred from spinal injection (Ireland; Duboff, 1920).

Benzyl Alcohol, N.N.R. (Phenmethylol), $C_6H_5CH_2OH$, was introduced by Macht, 1918. Its toxicity is low, since it is largely converted into benzoic and then into hippuric acid (Diack and Lewis, 1928). Intravenous injection causes vasodilatation. The urine flow may be increased or diminished (Gruber, 1924). The pure substance is irritant and somewhat corrosive, but watery solutions which contain up to 4 per cent are not irritant. Hirschfelder, 1920, claims that injections of benzyl alcohol solutions in man are unsatisfactory; that the anesthesia is uncertain and is often followed by subcutaneous edema and local pain. It is used for injection anesthesia, generally as 1 to 4 per cent solution. This is also anesthetic on mucous membrane, but the action is rather brief (Sollmann, 1919). Benzyl alcohol is fairly effective against the itching of dermatitis; for instance, in the milder grades of "mustard gas" poisoning. It is used as a 10 per cent ointment in lard; or as a mixture of equal volumes of benzyl alcohol, alcohol and water (Hess). Benzyl alcohol is soluble in all proportions in oil.

Benzyl Carbinol (Rose Oil), $C_6H_5C_2H_4OH$. Hjort and Eagan, 1919, find its anesthetic action more powerful than that of benzyl alcohol. Its toxicity is about the same, but it is more stable and sufficiently soluble for therapeutic use. Its isomer, phenyl-methyl-carbinol, is more effective, but also more toxic. It is unstable, and therefore not practical (Hjort and Kaufmann, 1920).

Butacaine Sulfate, U.S.P., *Butyn Sulfate*, a procaine derivative, containing butyl in place of ethyl, and propanol in place of ethanol. Its properties differ practically from those of procaine, for it is absorbable from mucous membranes. It is more toxic even than cocaine, and is therefore not advisable for injections, but it is useful in ophthalmic operations (2 per cent) and in nose and throat work (2 to 5 per cent). It is easily soluble in water· the solutions may be sterilized by boiling. It is somewhat irritant to the conjunctiva.

Butyl Aminobenzoate, U.S.P., *Butesin*. A sparingly soluble and slowly absorbable anesthetic, used as dusting powder; more effective than ethylaminobenzoate.—*Butesin picrate* is used on burns and ulcers as 1 per cent ointment.

Carbinols.—A series of phenyl-carbinols was investigated by Hirschfelder *et al.*, 1920 (see below, Saligenin). All are anesthetic.

***Cocaine Hydrochloride,** U.S.P., occurs as colorless, transparent prisms; or flaky, lustrous leaflets, or white, crystalline powder. Very sol. in water (1:0.5). Solutions may be colored with sodium fluorescein, 1 mg. per Gm. of cocaine. *Incompatible* with alkalis, sodium borate (not boric acid) and silver nitrate. Solutions decompose on keeping (a 15 per cent solution in Dilute Alcohol is said to be permanent; Wintersteiner, 1906). Contrary to older statements, they are not materially decomposed by boiling. Cocaine is obtained from the dried leaves of Erythroxylon species, shrubs indigenous to Peru and Bolivia, and cultivated in tropical countries. Ceylon coca contains mainly cocaine; Java coca contains only other ecgonine derivatives (Jong, 1911). Cocaine may also be prepared synthetically. The free alkaloid, *Cocaina*, U.S.P., is slightly sol. in water (1:600); sol. in organic solvents and oils, and in 80 to 100 parts of liquid petrolatum. It is used especially in ointments or solutions in oil.

Cycloform, isobutyl p-aminobenzoate, is a sparingly soluble local anesthetic. Dose, 0.1 to 0.2 Gm.

Diothane Hydrochloride, N.N.R., Piperidinopropanediol-di-phenyl-urethane hydrochloride, introduced by T. H. Rider, 1933, is claimed to be twice as potent as cocaine on mucous membranes, and three times as potent as procaine on injection (Rider and Cook, 1938). Its action is more prolonged, and is followed by a period of analgesia. It dissolves slowly in water, up to 1 per cent. It is used as 0.5 and 1 per cent solution, but it is so damaging to tissues that its employment appears inadvisable (Beutner and Calesnick, 1942). Its toxicity by hypodermic injection is about that of procaine, but by vein it is three times more toxic (Rider, 1933).

Ethyl Aminobenzoate, U.S.P. (Benzocaine, Anesthesine, $C_6H_4NH_2.COO(C_2H_5)$ 1:4). Small white or colorless crystals, or crystalline powder. Odorless. Very slightly sol. in water (1:2500), freely sol. in alc. (1:5), almond oil (exp.) or olive oil (1:50 at 25°C.). Sol. in dil. acids. Dose, 0.3 to 0.6 Gm., 5 to 10 grains. *Ethyl Aminobenzoate Ointment,* U.S.P., contains 5 per cent in White Ointment.

Eucaine Hydrochloride, U.S.P. (trimethyl-benzoxypiperidine; beta-eucáine hydrochloride). White, crystalline powder; odorless. Sol. in water (1:30) and alc. (1:35). Dosage, locally, one to two times that of cocaine. The anesthetic effect is perhaps slightly slower and weaker, and the irritation considerably greater, than with the same concentration of cocaine. The pupils are not dilated; the tissues are rendered hyperemic. The toxicity is four-tenths that of cocaine. Toxic doses cause convulsions, central vagus stimulation and direct cardiac depression, with fall of blood pressure (Orr, 1916).

Holocaine: see *Phenacaine.*

La′rocaine Hydrochloride, N.N.R., differs from procaine in side chains. It is claimed that it is effective from mucous membranes as well as by injection, and that the action is somewhat more lasting. It is used in the same concentrations as procaine. L. L. Mayer, 1935, recommends it for eye work, as its instillation produces prolonged and lasting anesthesia, without undesirable effects on the conjunctiva, intra-ocular tension, pupils or accommodation.

Met′ycaine Hydrochloride, N.N.R., Benzoyl-gamma-[2-methylpiperidino] propanol hydrochloride. Active from mucous membranes as well as by injection (C. L. Rose *et al.,* 1930). Toxicity, intravenously about three times that of procaine; subcutaneously, it is 20 to 30 per cent more toxic, but the anesthesia lasts about 45 per cent longer (C. C. Pfeiffer and Grant, 1944). Dosage for mucous membranes: eye, 2 per cent; nose and throat, 2 to 10 per cent; urethra, 1 to 4 per cent; dental nerve blocking, 2 per cent; infiltration of small areas, ½ to 1 per cent. A ¾ per cent solution is about the clinical equivalent of 1 per cent procaine, and lasts somewhat longer. Conjunctival anesthesia with 2 per cent procaine lasts eight to ten minutes, with no cycloplegia or corneal injury, nor increase of intra-ocular tension (J. R. Newcomb, 1931). Freely soluble in water. Solutions are stable on boiling and exposure to light and air. Marketed as powder and capsules. It was introduced by S. M. McElvain, 1927.

Mono′caine Hydrochloride is closely related to procaine. It appears to be about a third more potent in anesthetic action and in toxicity. The more soluble *Monocaine Formate* is used for spinal anesthesia.

No′vocaine Hydrochloride: see *Procaine Hydrochloride.*

Nu′percaine Hydrochloride, N.N.R. (introduced as percaine), is a complex amine derivative of quinoline. It was introduced as a local anesthetic in 1929, having been studied especially by Uhlmann, and by Lipschitz and Laubender. A later study of Bond and Bloom, 1931, concerns especially the toxicity. Gessner and Nauheimer, 1930, cover the pharmacology and toxicity. Nupercaine is three to ten times more effective and particularly much more lasting than cocaine, even from mucous membranes, and also about two to five times more toxic. Addiction has not been reported. It may prove an acceptable substitute for cocaine for mucous membranes; for injections, procaine appears preferable, because of its much greater margin of safety. The *local vascular* changes are so slight that the statements are contradictory. There is no immediate *irritation;* for instance, of the sciatic nerve; but local gangrene has occurred. The *clinical fatalities* were reviewed by E. L. Keyes and McLellan, 1930. They were usually due to gross errors of dosage. Death has occurred from the injection of 90 mg. (about 1.5 mg. per Kg.); on the other hand, 750 and 1500 mg. (about 25 mg. per Kg.) have been survived. These doses agree with the *fatal dosage in animals. The symptoms of clinical poisoning* resemble those of other anesthetics (Keyes and McLellan). *Clinical spinal injections* may cause vasomotor collapse, headache, nausea and vomiting (H. Ziegner, 1929). A hypersensitive patient responded with marked chemosis to conjunctival instillation of 1:500 (Perera, 1940). Nupercaine is marketed as the hydrochloride, a white crystalline hygroscopic powder, soluble in water (2:1), freely soluble in alcohol. The solutions may be autoclaved, but even dilute solutions are precipitated by traces of alkali, and therefore by prolonged contact with ordinary glass A few drops of dilute acid may therefore be added (to *p*H 6.2). This is said to enhance the anesthetic action.

Orthocaine, methyl amino oxybenzoate, Orthoform. Dose, 0.1 to 0.2 Gm., 1½ to 3 grains. Sometimes produces inflammatory reaction (McCleave, 1914).

Phenacaine Hydrochloride, U.S.P.; *Holocaine Hydrochloride.* The hydrochloride of ethenyl-p-diethoxydiphenylamidine. Small, colorless crystals, permanent in air; odorless; faintly bitter taste; producing transient numbness on the tongue; sol. in water (1:50), freely sol. in chloroform. Aqueous solutions occasionally become turbid when boiled in glass vessels (alkali of glass causing precipitation). Dosage, for eye, 1 per cent. Its pharmacology and that of its derivatives has been studied by Jeleff *et al.,* 1943. Anesthetic action about as strong as cocaine, but more rapid (anesthesia in half a minute); more toxic. No effect on vessels has been reported (Gjessing, 1915). It is not mydriatic.

Pontocaine Hydrochloride: see *Tetracaine.*

***Procaine Hydrochloride,** U.S.P., Prócaine, *Nóvocaine* (aminobenzoyl-diethyl-aminoethanol hydrochloride). Colorless needles. freely soluble in water (1 Gm. in 1 cc.); sol. in 30 parts of alcohol. The *nitrate* is compatible with silver salts. Dose, by subcutaneous injection, up to 1 Gm.; by intrathecal injection, up to 0.15 Gm. Occasionally, toxic effects occur even with small doses (0.01 to 0.13 Gm.); while in other cases up to 3 Gm. have been used safely. There is no definite ratio between the toxicity of procaine and cocaine, since this depends on the rate with which they enter the circulation, as procaine is rapidly destroyed in the liver. Epinephrine diminishes the toxicity, even by intravenous injection, probably by cardiac stimulation (Hatcher and Eggleston, 1916). By intradural injection the relative depressant effects of procaine and cocaine on blood pressure and respiration were about equal. Renal irritation is not uncommon after local use of 5 to 10 per cent, but disappears in a few days (Morian, 1915). Procaine convulsions in guinea pigs may be prevented by para-aminobenzoic acid, although this does not antagonize local anesthesia (R. K. Richards and Kueter, 1946); nor does it prevent procaine convulsions in rats and mice (Sollmann and Estable). *Procaine dermatitis* is frequent in dentists, from leaky syringes. It is strictly local and usually seems to require repeated contact and hypersensitivity, demonstrable by cutaneous tests (C. J. Lane, 1921; R. C. Morris, 1921). Skin which is allergic to procaine is also allergic to most of its derivatives, such as butyn, larocaine, monocaine, pontocaine and tutocaine; but not to derivatives that lack the aromatic amino group, such as alypine, apothesine, metycaine and stovaine (Orland *et al.*, 1944). J. Rosenbloom, 1922, reports that the use of a 5 per cent ointment against rectal pruritus resulted in marked edema, especially of the face, resembling nephritic edema.

The esterase of the blood hydrolyzes procaine to *para aminobenzoic acid* (Legge and Durie, 1942). This antagonizes the bacteriostatic action of *sulfonamides*, even with clinical applications (O. L. Peterson and Finland, 1944). Derivatives of procaine also have this effect (C. A. Lawrence and Goetchius, 1944). Metycaine does not and is at present the best available substitute (C. C. Pfeiffer and Grant, 1944).

Conversely, sulfonamides, in the concentration ratio of 6:1, antagonize the effects of procaine, such as on excised intestines and the local anesthetic action (R Hazard, 1946).

Procaine Derivatives.—A series of aromatic analogs were studied by J. Braun and Kirschbaum, 1919. The local anesthetic potency of the alkyl para-aminobenzoates correlates strikingly with their surface tension and partition coefficients (R. Adams *et al.*, 1926).

Propáesin (propylaminobenzoate) is difficultly soluble. Dose, 0.25 to 0.5 Gm.

Psicaine (dextro-cocaine) was investigated pharmacologically by Ishibashi, 1926. It potentiates with epinephrine.

Saligen'in (salicyl alcohol, salicain), $C_6H_4.OHCH_2OH$. Hirschfelder *et al.* found this the most effective, and the least toxic and irritant, of the phenyl-carbinols so far studied. Its toxicity is much lower than that of the procaine-apothesine type. In tonsillectomy, 2 per cent saligenin appeared as effective as procaine.

Sto'vaine (benzoyl-ethyldimethyl-aminopropanol hydrochloride). *Amylocaine Hydrochloride,* B.P. Dose (subcutaneous injection), 20 to 50 mg.; (intrathecal injection), 20 to 100 mg. Colorless scales, extremely soluble in water, or in 5 parts of alcohol. Dosage, locally, as for cocaine. Anesthetic action slightly stronger, irritant action (hyperemia) much greater, toxicity two-thirds that of cocaine. No effect on pupil. It has been used especially for spinal anesthesia, in combination with strychnine (T. Jonnescu, 1909). The immediate danger may be somewhat less than with cocaine, although it is not negligible. The local injury is much greater. Spiller and Leopold, 1910, and Consoli, 1913, observed degenerations in the nerve roots and cells after subdural injections of stovaine. The immediate paralysis is more extensive than with cocaine, involving muscular movements (Santesson, 1906) and spinal reflexes (Adler, 1906). On the circulation, it causes in dogs quickened pulse and fall of blood pressure (Kamenzove, 1911). The kidneys are also rather irritated, especially if albuminuria was previously present (Schwartz, 1907; Chiaie, 1913). The liver is not affected (side actions, Seifert, Nebenwirk, 1915, p. 91; lumbar, p. 109). A comparative study of the local anesthetic actions of stovaine and its homologues was made by Symes and Veley, 1911. The literature of accidents is reviewed by M. I. Smith and R. A. Hatcher, 1917. Death occurs by simultaneous and independent paralysis of the heart and respiration. Stovaine disappears rapidly after injection into the blood stream, and but little is excreted It is removed and presumably destroyed by the liver. In over 1000 cases of stovaine spinal anesthesia, about 30 per cent showed more or less by- or after-effects. One patient had respiratory failure; seven patients transient paralysis (Muenchmeyer, 1908).

Tetracaine Hydrochloride, U.S.P. (**Póntocaine Hydrochloride,** Amethocaine Hydrochloride, Pantocaine), is related to procaine. Its local actions are similar. It is effective with lower concentrations, especially from mucous membranes (Runge and Schmidt, 1931). Its toxicity on injection is ten times greater than that of procaine. It is used chiefly for surface anesthesia on the conjunctiva (0.5 per cent) and nose and throat (2 per cent); also in spinal anesthesia (1 to 2 cc. of 1 per cent).

Tro'pacocaine Hydrochloride (benzoyl-pseudo-tropeine) occurs in Javanese coca, but the commerical is synthetic. Colorless needles, readily soluble in water. It destroys the vasoconstrictor action of epinephrine. Dosage, locally, one or two times that of cocaine. Anesthetic action about the same; irritation greater; toxicity one-half that of cocaine; less mydriatic; more stable. It is used especially for spinal anesthesia (Stanley, 1916).

Tútocaine Hydrochloride, N.N.R., is a procaine derivative, effective from mucous membranes, as well as by injection, but toxicity (intravenous) is four times that of procaine, and death has been reported from 8 cc. of 2 per cent urethral injection. Dosage, for mucosae: eye, nose and throat, 2 to 5 per cent; urethra, 0.5 to 1 per cent; hypodermically, 0.2 per cent.

Yohimbine, an alkaloid isolated by Spiegel, 1896, from the bark of Yohimbehe tree (Apocynaceae; West Africa), appears to be identical with quebrachine (Fourneau and Page, 1914; Hamet, 1927). As a local anesthetic it has about the same potency as, but is more lasting tihan cocaine. It is less toxic, but much more irritant. Mydrasis, occurs without loss of accommodation. The vessels are dilated. Intestines, excised or *in situ*, and bladder are stimulated by small, depressed by large, doses (A. Loewy and Rosenberg, 1914). Solutions are unstable. The *systemic effects* vary with the dose and method of administration. Large doses intravenously *reverse epinephrine* and dilate the renal vessels. It does not interfere with the pressor response to electric sympathetic stimulation, or of nicotine or acetylcholine in atropinized animals (Koppanyi, Linegar and Herwick, 1943). It diminishes other epinephrine effects (M. Hutchinson *et al.*, 1942). Slow injection produces slow rise of blood pressure by cardiac stimulation. Intraspinal or suboccipital injection produces anesthesia and lowers the blood pressure (F. Mercier and Delphaut, 1936). The spleen is dilated by large, constricted by small, doses (Bariéty and Kohler, 1939). The autonomic actions were studied by P. Weger, 1929. When it is given by the mouth or hypodermically in moderate doses, it produces general *vasodilatation* in the skin, mucous membranes and particularly in the *sexual organs*. In consequence of the latter, and perhaps by a direct action on the spinal centers, it produces erection. It does not seem to stimulate the production of spermatozoa or sexual desire. It does not increase the rate of reproduction in mice (Rumry, 1918). The effect is not produced by therapeutic doses in man (5 mg. or $\frac{1}{12}$ grain), although it has been promoted as an aphrodisiac. The reports of clinical improvement after several weeks are probably explainable by suggestion. In female rats, small doses, 1 to 2 mg., provoke prolonged estrus; 3 to 4 mg.

produce *pseudopregnancy.* These effects have been attributed to stimulation of the *anterior pituitary* (Fugo and Gross, 1942). A 1:1000 solution ingested by rats as drinking water over three months was nontoxic (F. F. Yonkman, 1944). Yohimbine has been proposed for lowering abnormally high blood pressure; but Lawrence, 1912, found that it may produce a further rise, with dangerous symptoms. Small doses lower the *temperature* of normal rabbits, and also after destruction of the heat centers. Larger doses are antipyretic against cocaine or "tetra" fever (Yamauchi, 1928). Large doses produce psychic excitement, cerebral congestion, vertigo, gastric disturbance; and in rabbits, marked injury of the renal epithelium (Huebner, 1912). Toxic doses produce general stimulation and subsequent paralysis of the nervous centers, particularly in the medulla; and complex effects on the cardiac muscle (F. Mueller, 1907; J. Tait, 1910). The coronary vessels are not affected (Rabe, 1912); or they are dilated (F. Meyer, 1912). Death occurs by respiratory paralysis (literature, Strubell, 1906).

Ethyl yohimbine was studied by A. G. Young and Yonkman, 1929.

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DRUGS ACTING PERIPHERALLY ON THE AUTONOMIC SYSTEM

A variety of poisons act peripherally on the several portions of the involuntary or "vegetative" nervous system, in a more or less specific manner. It appears advisable to premise their individual consideration by a more general exposition.

Anatomic and Physiologic Relations.—The "autonomic" system (Langley, 1921) includes all the functions subject to involuntary nervous control—the smooth and cardiac muscles and the glands. They are capable of functioning automatically, when all connections with the cerebrospinal axis are severed, but their functions are normally regulated, augmented or inhibited by central tonic impulses of varying intensity. The distinctive *anatomic* peculiarity of the automatic nerves is that they pass through relay ganglionic cells, situated outside the central nervous axis. The cells of the sympathetic division are mostly collected into the chain of sympathetic ganglia, including the splanchnic ganglia; those of the parasympathetic division are mostly situated on and in the organs. Each nerve fiber has but a single relay, although it may pass through a number of ganglia.

The two divisions of the autonomic nervous system, the *cholinergic* or *parasympathetic* and the *adrenergic* or *orthosympathetic*, generally called the *sympathetic*, differ in their response to drugs; in embryologic derivation in the site of origin in the central nervous system; in the location of the ganglionic cells, and in the fact that both divisions may innervate the same cell, generally in antagonistic directions.

Distribution and Function.—The two divisions are usually antagonistic, a given organ as a rule receiving its innervation from both divisions, one being augmentor, the other inhibitory. The *orthosympathetic division* is generally augmentor to the blood vessels and to the organs derived from the ectoderm; the *parasympathetic system* is augmentor to the organs derived from the endoderm. The inhibiting innervation is generally just the converse. (Circular and longitudinal coats have the same—not reciprocal—innervation; Gaskell). The innervation of the *sweat glands* occupies a peculiar position; anatomically, it is purely sympathetic, but it reacts pharmacologically as if it were purely parasympathetic. The *nictitating membrane* of the cat, with purely sympathetic innervation, also reacts to cholinergic drugs and atropine (review, C. W. Darrow, 1943). The *uterus* is also exceptional: its sympathetic innervation responds to both classes of poisons. It must be remembered, however, that the anatomic evidence of the origin of the autonomic nerves is in some respects inconclusive. The designations "cholinergic" and "adrenergic," introduced by Dale, give a consistent classification (review, O. Loewi, 1945).

The *innervation of glands* is analogous to the muscular innervation; the glands derived from the epidermis (sweat) receive their augmentor supply from the sympathetic; the parasympathetic augments the endodermal glands (pancreas, gastric, mucus, etc.). The salivary glands probably have cells derived and innervated from both systems.

The most important augmentory and inhibitory innervations are:

Vasodermal System.—Augmentory, adrenergic; Inhibitory (so far as they exist), cholinergic.

Genital System.—(Uterus and Ureter.) Augmentory and inhibitory, both adrenergic.

Intestinal Sphincters.—Augmentory, adrenergic; inhibitory, cholinergic.

Intestinal Muscle.—Augmentory, cholinergic; inhibitory, adrenergic.

Esophagus and Cardiac Sphincters.—Augmentory and inhibitory, both cholinergic.

Heart and Vessels.—Augmentory, adrenergic; inhibitory, cholinergic.

Iris Sphincter and Ciliary Muscle.—Augmentory, cholinergic (tectal division); *Iris radial,* augmentory, adrenergic.

Autonomic Ganglia of Both Divisions.—Augmentory, cholinergic.

Pharmacologic Reactions of the Autonomic System.—The orthosympathetic and parasympathetic ganglia react alike toward poisons, for instance, nicotine. Beyond the ganglia the reactions to drugs are often more or less strictly confined to one or the other innervation; *i. e.*, peripheral pharmacologic reactions tend to be either "sympathomimetic" (Barger and Dale, 1910), as epinephrine, cocaine and ergotoxine; or "parasympathomimetic" (Langley), as pilocarpine, muscarine, choline, physostigmine and atropine. It appears that these systems are normally activated by specific neurohormones belonging to these groups, so that Dale, 1934, designated the orthosympathetic system as "*adrenergic*" and the parasympathetic as "*cholinergic*." This suggests a fundamental difference in the physico-chemical characteristics of the receptive mechanism of the two systems, but this is not absolute: A number of poisons act only on certain parts of one or both divisions; and even the most specific of the drugs, such as epinephrine or acetylcholine, may apparently have their actions transferred to the contrary division under certain conditions.

Pharmacology of the Parasympathetic (Craniosacral) Division.—This is stimulated by choline and its esters, pilocarpine, muscarine and indirectly by physostigmine (eserine). It is paralyzed by atropine, which is therefore antagonistic to all the other drugs named. If a sacro-cranial function is exposed simultaneously to the depressant action of atropine and to the stimulant action of one of the other drugs, the end result depends on the nature and quantity of the drug, and upon other conditions. The centers of the parasympathetic system are stimulated by picrotoxin.

The principal results of parasympathetic stimulation consist in: slowing of the heart; constriction of the pupil; bronchial spasm; contraction of intestine and uterus; increase of practically all centrally innervated secretions (sweat, saliva, mucus, gastric, pancreatic, etc.; not urine, bile, milk or the internal secretions). These are the main effects of pilocarpine, muscarine and physostigmine. *Craniosacral depression* (atropine) produces precisely the opposite results.

Discrepancies of Parasympathetic Poisons.—One of the most marked is the response of the retractor penis muscle of the dog: stimulation of the nerves gives inhibition; pilocarpine, contraction. Differences of degree of effect occur, most striking in small intestines.

Pilocarpine stimulates some sympathetic innervations: sweat glands, uterus, contraction or dilatation of arterioles, contraction of spleen. Atropine also paralyzes some sympathetic innervations: submaxillary secretory; sweat glands; skin glands of frog; secretory fibers of the prostate; and antagonizes pilocarpine wherever that acts. Gohara claims that it also abolishes the contractor effect of epinephrine on rabbit's uterus.

Pharmacology of the Orthosympathetic Division.—*Epinephrine*, the alkaloid of the suprarenal gland, produces a pure peripheral stimulation, restricted exclusively to the sympathetic system, but involving the entire distribution of this system (with the exception of the sweat glands). In other words, the effects of typical doses of epinephrine on a given organ correspond precisely to the stimulation of its sympathetic nerve supply (Lewandowsky, 1899; Langley, 1901; Elliott, 1905). The action of epinephrine is therefore augmentory or inhibitory, according to whether the sympathetic impulses are augmentory or inhibitory. The *augmentory reactions* include constriction of most of the arteries and consequent rise of blood pressure; stimulation of the cardiac accelerator; dilation of the pupil; contraction of the plain muscle of the orbit; flow of sympathetic saliva and of tears, not readily abolished by atropine; erection of hair, etc. *Inhibitory reactions* occur only in organs whose function is augmented by parasympathetic stimulation (C. W. Darrow, 1943). They concern the tone and rhythm of the contractions of the stomach, intestine, biliary and urinary bladder (cat), and of the virgin uterus of the cat. *Cocaine* increases the peripheral excitability of the sympathetic system without being directly stimulant.

Divergences of Epinephrine from Sympathetic Stimulation.—The only structures markedly influenced by sympathetic stimulation and not by epinephrine after nerve section are the sweat glands in the cat and some other mammals. There is also an instance of parasympathetic stimulation by epinephrine: the pulmonary arteries of frog and turtle are constricted by epinephrine and by vagus stimulation; antagonized by atropine; and they do not constrict by sympathetic stimulation (Luckhardt and Carlson, 1921).

Quantitative differences are more numerous; in cases where sympathetic stimulation causes both augmentory and inhibitory effects, the predominance with epinephrine may be the reverse of that with nerve stimulation.

Removal of the entire sympathetic system from cats and dogs is compatible with life and with normal functioning and activity (Cannon, 1929), but such animals adjust less perfectly to a number of conditions, such as emotional excitement, heat or cold.

Peculiarities of Species.—Certain of the sympathetic reactions vary with the species of animals, being augmentory in some and inhibitory in others (urinary bladder anal sphincter). The sympathetic reaction of the uterus varies according to its physiological state; in the cat, the virgin uterus is inhibited, while the pregnant uterus is stimulated. All these peculiarities are reproduced exactly in the reaction to epinephrine, thus furnishing the most striking illustrations of its sympathomimetic action.

Other Drugs with Sympathomimetic Action.—Similar actions are possessed by a large number of primary and secondary amines, the simplest being the primary fatty amines (amylamine, etc.). There are quantitative differences between these. The relative effect on the different sympathetic distributions does not go parallel; nor is there any parallelism between augmentory or inhibitory innervations. The intensity and specificity increase as the amines approach the structure of epinephrine (Barger and Dale, 1910). A compilation of the amines and their relation to pharmacology is also given in Guggenheim's book.

Peripheral Sympathetic Paralysis: Ergotoxine.—The active alkaloids of ergot (in large doses) destroy the response of the augmentory sympathetic impulses, and in larger doses also the inhibitory sympathetic impulses (Röthlin, 1929; Dale, 1906). It therefore prevents the vasoconstrictor action of epinephrine, but not ordinarily the inhibitory action on the intestine or uterus. Similar effects result from certain synthetic phenoxyethylamines and dioxane derivatives prepared by Fourneau ("F 833" and "F 933"). The most distinctive "sympatholytic" action appears to be exerted by *dibenzyl-beta-chloroethylamine* and related compounds (M. Nickerson and Goodman, 1946).

The **autonomic ganglia** of both divisions are cholinergic; they are stimulated by the parasympathetic stimulants and depressed by atropine and by epinephrine.

The best evidence is furnished by the action potentials in the postganglionic nerve trunks (for instance, the cervical sympathetic) in response to natural or test stimulation of the preganglionic trunks (Marrazzi, 1939). These action currents are increased by pilocarpine and depressed by atropine, with mutual antagonism in the ratio of A:P::1:10. Pilocarpine in the ordinary doses only increases the ganglionic response and never initiates ganglionic activity. Excessively high concentrations of acetylcholine inhibit the response. Epinephrine, ephedrine and their derivatives in full doses inhibit synaptic transmission through the ganglia (Marrazzi, 1940). Small doses of epinephrine improve it (Bulbring and Burn, 1944). Cannon and Rosenblueth, 1937, concluded that sympathetic ganglia are stimulated and then depressed by acetylcholine, and that prostigmine potentiates electrical stimulation of the preganglionic fibers. It has no direct effect on the postganglionic fibers, but depresses their response to preganglionic stimulation by leading to excessive acetylcholine accumulation in the ganglia. *A difference,* however, appears to exist between the parasympathetic and sympathetic ganglionic synapses, in their reaction to *deficiency of calcium ions;* for intravenous injection of sodium citrate temporarily paralyzes the parasympathetic path to the pupillary sphincter of the cat, at the ganglionic synapsis, but has no effect on the pathway for pupillary dilatation, for vasoconstriction and other sympathetic reactions (G. D. Shafer, 1939).

Nicotine paralyzes all the ganglionic synapses of both the parasympathetic and the orthosympathetic nerves (often after fleeting primary stimulation). The paralysis is so specific that it has proved of great value, especially in the hands of Langley, for locating the site of these synapses. Nicotine, whether it is applied locally or systemically, abolishes the response to stimulation of the preganglionic fibers, while the postganglionic fibers respond normally.

Strychnine, acetylcholine, choline, arecoline, physostigmine and potassium ions, like nicotine, stimulate and then depress all autonomic ganglia. Curare, sparteine, large doses of atropine, methenamine iodomethylate and the Fourneau sympatholytics depress without precedent stimulation. The depression is antagonized by stimulant doses of nicotine. The susceptibility to paralysis is in the following order: *first,* cardio-inhibitory; *second,* chorda-secretory, sweat, pilomotor, pupil dilator and constrictor, probably also bulbar and sacral vasodilators; *third,* nictitating membrane and cutaneous vasodilators; *fourth,* epinephrine secretors and abdominal vasoconstrictors.

Localization of Action.—The possible points of attack in the peripheral distribution of the autonomic system may be grouped as (1) The ganglionic elements; (2) the nerve endings, including the terminal fibrils; (3) the receptive mechanism or excitability of the terminal cell; (4) the responsive mechanism of the cell, *i. e.,* the contractibility or secretory activity.

The *methods of analysis* rest upon the general principle of localizing depression by the application of stimuli, and stimulation by producing depression or paralysis, centrally and peripherally to the suspected site of action. This is simple for the ganglia, when these are situated apart from the other structures; but when they are intermingled, less direct and correspondingly less decisive methods must be employed. The difficulty increases with the more peripheral structures. Stimulation of the nerve fibrils and endings may be excluded by section and degeneration; but the converse does not hold, *i. e.,* disappearance of response after degeneration does not prove that the stimulation was in the nerves; for section of the nerves also causes degeneration of the muscle fibers, and consequently changes in their excitability. The degeneration method could not throw light on the site of a depressant action. This, and still more the distinction between the receptive and the responsive mechanism, rests upon indirect methods. It is tempting to aid the localization by the use of antagonistic drugs; but this is likely to mislead, since the antagonism of drugs is influenced by factors other than their normal site of action (Magnus, 1908). Because of these difficulties, the current views as to the localization of autonomic actions are tentative rather than final; they serve to classify rather than explain the observations. Their general tendency is toward simplification: It appears that the nerve fibrils and endings are not concerned in the specific autonomic reactions; that the ganglia play a minor share, except with the nicotine group; and that therefore the autonomic poisons act almost exclusively directly on the receptive or responsive mechanism of the muscle or gland cell.

The Ganglia.—Localization in these structures is illustrated by the effects of nicotine on the heart. After the injection of the drug stimulation of the vagus trunk fails to slow the heart, but stimulation of the postganglionic fibers, in the sinus, produces the normal slowing. The nicotine must therefore have paralyzed something between these points, *i. e.*, the ganglia.

The ganglia of invertebrates (*f. i.*, Sipunculus, Magnus, 1903; cardiac ganglia of the king-crab, Carlson, 1906) are susceptible to the whole series of autonomic drugs. With vertebrates, however, wherever the ganglia can be separated with sufficient sharpness, they do not seem to be very susceptible to autonomic poisons other than the nicotine group, but they are somewhat cholinergic.

Functions of the Ganglion Cells.—These are evidently the nutrient centers of the nerve fibers. With invertebrates they may also act as reflex centers; but there is no clearly demonstrated instance of this function in vertebrates. As early as 1868 Maurice Schiff (Leçons sur la Physiologie de la Digestion, pp. 394–396) insisted that the conception of sympathetic ganglia as "peripheral reflex centers" was without experimental foundation. On the whole, the facts seem in harmony with Gaskell's view that the ganglion cells of the autonomic system are connector elements, analogous to the pyramidal cells of the motor system, but transposed to the periphery.

The motor end plates of striped muscle are interpreted by Eichler, 1938, as ganglion cells with normally latent rhythmicity, which mav be made active by veratrine.

Nerve Fibrils.—There is no conclusive evidence that any specific autonomic poisons act on the "nerve endings" that degenerate after section of the nerves; and the evidence of excised organs is distinctly against this mechanism. Nerve fibers, where they can be reached directly, are practically unaffected by most of the specific autonomic poisons. It is therefore improbable that the finer terminal fibrils, which seem to be mere continuations of the axis cylinders, should be the site of the specific actions. They differ from the larger fibers in permeability, but this would cause only quantitative differences. Direct evidence against the nerve fibrils is furnished by the persistence of the responses to autonomic drugs, in excised organs after the excitability of the nerve fibers has been lost. The effects of a number of autonomic drugs, notably epinephrine and acetylcholine (Cattell and Wolff, 1935), can still be evoked after complete degeneration of the nerve, following division of the nerve trunk. This localizes their action definitely beyond the terminals that are in nutritive connection with the nerve.

The interpretation of the converse phenomenon, disappearance of the drug response as the result of degeneration, is not so decisive. The effects of pilocarpine, for instance, can be evoked like those of epinephrine, after degeneration, *i. e.*, when stimulation of the nerve trunk is ineffective. After a time, however (six weeks for sweat; Anderson and Langley, 1904), the response becomes less efficient, although the muscle still responds to electric stimulation. This probably means that in the end the muscle cell also deteriorates, "atrophies," when it is not functionally used; and that this deterioration abolishes its excitability by pilocarpine before it abolishes the contractor response to direct electric stimulation. The protoplasm of motor end plates shows morphologic changes after the nerve is severed, and they may disappear in about six months (review, S. S. Tower, 1939).

The Receptive Mechanism.—Since degeneration of the nerve endings does not interfere with the typical effects of epinephrine, this must act on the muscle cells directly. This conclusion encounters the difficulty that epinephrine acts in reverse directions on smooth muscle in different locations, producing contraction in one place and relaxation in another. The smooth muscle in both cases appears to be identical, and reacts in a uniform direction to other stimuli, such as electric shocks, or poisons like barium. They differ only in their innervation, and this difference is reproduced faithfully by epinephrine. Since the degeneration experiments clearly prove that epinephrine does not act upon the nerves themselves, it becomes necessary to assume the existence of some intermediate mechanism, related to the innervation, but not trophically dependent upon it. Presumably all specific autonomic poisons act through the mediation of receptive mechanisms which differ specifically for ortho- and parasympathetic innervations, probably by releasing epinephrine or acetylcholine at the synapse (review, O. Loewi, 1945).

The mediating mechanism may be regarded in several ways: (*a*) as a morphologic structure; (*b*) as a chemical receptive substance or side chain; (*c*) as a physical system. The available facts do not permit a decision between these; indeed, the theories themselves lack so much in detail that a decisive attitude toward them would not be justified. Consequently, there is an advantage in employing a noncommittal term, such as "*receptive mechanism*," for the entire concept; and restricting the more specific terms, "myoneural junction" (Brodie), "receptive substance" (Langley, 1905) and "synapse," to the special theories that they represent. Critical reviews of the older theories may be found in the reviews of Langley, 1921, and Sollmann, 1922.

The Responsive Mechanism.—The sharp separation of this from the receptive mechanism is of doubtful validity: The functions of excitability and contractility or secretion are so closely related that it is impossible to imagine a muscle that is excitable but does not contract; or one that contracts but is not excitable.

The actual presence of nerves is not necessary for the response to cholinergic or adrenergic drugs, for smooth muscles that are devoid of innervation, such as the chick amnion (Baur, 1928) and tissue cultures of embryonic intestine, contract with acetylcholine and relax with atropine and with epinephrine. The ingrowth of nerves may sensitize and in some cases reverse the response (J. Ferguson, 1940; E. Fischer, 1944).

The heart of the chick embryo does not respond to ordinary concentrations of acetylcholine until the vagus fibers have been developed (V. E. Henderson and Roepke, 1937); nor does acetylcholine inhibit cultures of the chick heart (Garrey, 1937), nor the heart of fundulus embryos until shortly after the nerve fibers have reached the auricles. This holds also for pilocarpine. The striped muscle contracture by acetylcholine, however, occurs before as well as after innervation (Armstrong, 1935).

Chemical Mediation of Autonomic Stimulation: "Neurohormones."—The demonstration that autonomic nerves liberate chemical substances in the end organs, which produce para- or orthosympathetic stimulation according to the kind of nerve stimulated, suggests that the mediation between nerve and cell consists in the specific chemical action of these substances (Dale), therefore called neurohormones by L. Fredericq, rather than in the physical transmission of an electric potential from the nerve to the effector cell. From their pharmacologic actions and chemical behavior, the neurohormones appear to be identical with acetylcholine and epinephrine or noradrenalin (arterenol) respectively, or at least to be closely related derivatives of these. They are presumably formed from relatively inactive relatives, choline and oxidized epinephrine, existing in or about the nerve terminals and cells, probably as reversible systems—esterification for choline, oxidation-reduction for epinephrine (review and bibliography, Bacq, 1934). The relatively slow response to autonomic stimulation speaks for an exclusively chemical mediation, but the high concentration of choline esterase in the nerve axons and at the synapses makes even rapid responses appear feasible (Nachmansohn and John, 1945). This does not exclude the possibility that the nerve impulse may produce potential changes directly, but of this there is no conclusive evidence.

Mornier and Bacq, 1935, argue that the mediation is ordinarily chemical, but that the electrical potential enters into play when chemical mediation is blocked, as by "933 F." Nor need it be supposed that autonomic drug stimulation can occur only through these neurohormones. Some drugs have a specific relation to them, which is clear for physostigmine-acetylcholine, still obscure for the cocaine-epinephrine sensitization, the atropine and ergotamine inhibition, and the ephedrine stimulation. Neurohormones are probably not involved in the response to drugs with nonspecific peripheral actions—barium, magnesium, nitrite; perhaps histamine, pituitary and thyroxin.

Parasympathetic Hormone.—The discovery of neurohormones started with the observation by O. Loewi, 1921, of a typical vagus effect by a Ringer perfusate from a frog heart that had been subjected to vagus stimulation. This was confirmed on the hearts of other vertebrates (*f. i.*, Riccitelli and Vita, 1928), and extended to parasympathetic innervation generally (review, Thompson and Collip, 1934). *Atropine*, which prevents motor or secretory response to the parasympathetic stimulation, and so the action of the hormone, does not interfere with the production of the hormone, but with its action (Loewi).

Smaller doses of atropine generally suffice to antagonize cholinergic stimulation by drugs rather than by electric stimulation of the nerve. In explanation Dale, 1934, suggests that "the nerve impulses liberate acetylcholine so close to the reactive structures that atropine cannot intervene, whereas it can prevent its access to them when it is artificially applied from without." Several new anticholinic agents are reported by Abreu *et al.*, 1946.

Identification of the Parasympathetic Hormone with Acetylcholine.—The pharmacologic and chemic reactions of the perfusate are characteristic of acetylcholine, especially the *specific sensitization by physostigmine* and related bases (neostigmine), so that dilutions which have practically no effect when used alone, produce strong parasympathetic stimulation when used together, in excised organs, or with intact circulation. Physostigmine also greatly prolongs the effects of acetylcholine, which are otherwise brief, especially on intravenous injection (*f. i.*, clinically, Ellis and Weiss, 1932). Physostigmine sensitizes by inhibiting the specific choline esterase which is present in all parasympathetic tissues, and which normally effects rapid hydrolysis of acetylcholine to choline, whose parasympathetic potency is $\frac{1}{500}$ or less that of choline (O. Loewi and Navratil, 1926).

The Physostigmine Test for Acetylcholine.—Using this principle, Fuehner, 1916 and 1918, introduced the physostigminized dorsal muscle of the leech as a specific test for acetylcholine, sensitive to 1:20,000,000,000 (Binet and Minz, 1934). The specificity was confirmed by Chang and Gaddum, 1933; it can be made quantitative by observing uniform conditions (Binet and Minz). Very dilute solutions of physostigmine are effective (1:40,000,000 *in vitro;* Engelhart and Loewi, 1930; 0.01 mg. per Kg. *in vivo*, optimal 0.05 mg. per Kg., G. W. Manning *et al.*, 1937). Conversely, 0.01 γ of acetylcholine may be demonstrated by the blood pressure reaction (Gibbs and Szelöczcy, 1932). Other parasympathetic innervations may be used as test objects: the chorda tympani, frog heart, excised intestine, etc.

The degree of physostigmine sensitization to acetylcholine varies with different organs. The sensitivity of leech muscle is increased more than a thousand times; that of frog rectus abdominis only five times (Chang and Gaddum, 1933). In the frog heart the response is not increased but prolonged (Loewi and Navratil, 1926). It has been suggested that the difference is related to the diffusion of acetylcholine; if this is slow there is more opportunity for destruction (A. J. Clark, 1937).

Physostigmine does not sensitize to other autonomic drugs, *f. i.*, pilocarpine, epinephrine, histamine, peptone; nor for choline itself (although it is utilized for the estimation of choline by previous acetylization). It is characteristic for choline esters, but may be considered practically specific for acetylcholine, since none of the other known esters approach this in the ratio of sensitization for different organs (Chang and Gaddum, 1935). Since this reaction applies to the "vagus substance" (Galehr and Plattner, 1927) and all the other parasympathetic perfusates, the identification of "*parasympathin*" or "*vagotonin*" with acetylcholine is considered practically assured, especially as acetylcholine is the only choline ester which has been isolated chemically from animal tissues (review, G. L. Brown, 1937). Physostigmine greatly prolongs the effects of acetylcholine, which are otherwise brief, especially on intravenous injection (*f. i.*, clinically, Ellis and Weiss, 1932). Removal of acetylcholine by *intravenous injection of choline esterase* prevents the transmission of nerve impulses to the pupil sphincter, so that the light reflex is abolished (Mendel and Hawkins, 1943). Physostigmine apparently competes with acetylcholine for the esterase, which combines with either, destroying them (A. Goldstein, 1944). A series of *synthetic bases related to physostigmine*, such as *neostigmine*, also produce this inhibition of acetylcholine esterase. It appears to be connected with the methylurethane side chain (Stedman and Stedman, 1931). Less potent inhibitions are caused by many unrelated substances: ergotamine (Mather, 1930), strychnine (D. Nachmansohn, 1938), or quinine; by local anesthetics (Adriani and Roverstine, 1941); by certain dyes, including gentian violet and methylene blue (Massart and Dufait, 1941); and by epinephrine oxidation products (Waelsch and Rackow, 1942). Epinephrine itself increases the synthesis of acetylcholine. The parasympathetic effects on epinephrine may be explainable by these actions on choline esterase (Torda and Wolff, 1944). *Nicotine* apparently desensitizes to acetylcholine.

Stimulation of cholinergic nerves liberates *thiamine* as well as acetylcholine (B. Minz, 1938). Thiamine and cocarboxylase inhibit choline esterase *in vitro* (Glick and Antropol, 1939), but the required concentrations are higher than exist in the serum and perhaps in the tissues. Biologic concentrations increase the synthesis of acetylcholine by homogenized frog brain (Torda and Wolff. 1944).

The choline esterase level of serum is very constant in a given individual (Milhorat, 1938), and in a variety of diseases. It is decreased in pregnancy and severe hepatic damage (Butt *et al.*, 1942).

Besides the *specific choline esterase*, which hydrolyzes only certain choline esters, there is *nonspecific choline esterase*, which hydrolyzes a variety of other esters, and is not materially concerned in the neurohormone function (Alles and Hawes, 1940; B. Mendel and Rudney, 1943). Both choline esterases are widely distributed. The superior cervical ganglion of cats contains them in about equal concentration. Most of the acetylcholine hydrolysis in sympathetic nerve trunks is accomplished by the specific esterase (C. H. Sawyer and Hollinshead, 1945). Frog brain contains a true choline esterase which is much more resistant to inhibition by physostigmine than is that of mammalian brain (R. D. Hawkins and Mendel, 1946).

Acetylcholine Synthesis.—The specific acetylcholine esterase perhaps accelerates the synthesis as well as the hydrolysis of acetylcholine. This two-sided reaction may constitute the chemical mediation of stimulation. While physostigmine inhibits the hydrolysis, it permits the synthesis of acetylcholine to proceed (F. H. Shaw, 1935).

Concerning the *site of the formation* of acetylcholine, it is suggestive that choline is a component of the lecithin molecule, which is abundant in *nerve fibers*. Binet and Minz, 1934, found that extracts of the vagus trunk give the acetylcholine test, which is materially greater if the nerve has been stimulated. The sciatic nerve gave a much smaller quantity and it was not increased by stimulation. Lissák, 1939, confirmed that acetylcholine or an analogous substance is liberated by stimulation of isolated parasympathetic nerves, of preganglionic nerves and of autonomic ganglia of both divisions, but not by sympathetic nerves. Stimulation of sympathetic nerves liberates a substance with epinephrine actions; stimulation of the sciatic nerve liberates both cholinergic and adrenergic substances. Quastel, Tennenbaum and Wheatley, 1936, found that acetylcholine or a related ester is formed on the addition of physostigmine to the fluid in which *brain sections* are suspended. The presence of glucose is essential for acetylcholine formation by brain sections (M. C. Sanz, 1943). Nachmansohn and Machado, 1943, report formation of acetylcholine by an enzyme extracted from brain and nervous tissue, in the presence of adenosine triphosphate, under anaerobic conditions. Extracts of nerves that have undergone Wallerian degeneration are much less effective (M. Berman and Nachmansohn, 1946). W. Feldberg and Mann, 1946, describe a complex enzyme system for the synthesis of acetylcholine in the central nervous system. This synthesizing ability is especially great for the cholinergic efferent nerves, small for afferent nerves.

The autonomic ganglia, sympathetic as well as parasympathetic, liberate acetylcholine (by the physostigmine test) on stimulation of their preganglionic fibers (W. Feldberg and Gaddum, 1933; V. E. Henderson and Roepke, 1934). With prolonged preganglionic stimulation of perfused superior cervical ganglion of the cat, the acetylcholine output starts at a high level, then falls rapidly for 20 to 60 minims, and then continues almost level (G. L. Brown and Feldberg, 1936). This has been cited as evidence that their stimulation occurs normally by this chemical mediation, since direct addition of acetylcholine stimulates ganglionic response with lower concentrations, although high concentrations are depressant (Cannon and Rosenblueth, 1937; Marrazzi, 1939); and with *oxygen lack* of the perfused stellate ganglion, there is practically parallel failure to respond to preganglionic stimulation to acetylcholine and to discharge spontaneous impulses (Bronk *et al.*, 1938). However, Lorente de Nó, 1938, 1940, found that the acetylcholine is not regularly released by stimulation of blood-supplied ganglia, but only after some departure from normal conditions, and then in extremely variable amounts; indicating that acetylcholine does not play an indispensable role in synaptic transmission (prolonged stimulation of the preganglionic fibers in dogs also decreases the potassium content of the ganglia; direct stimulation of the denervated ganglion does not do so; M. Vogt, 1936).

Choline Esterase Distribution in Nerve Structures.—Nerve trunks have a high choline esterase concentration. It has been shown in the giant nerve fiber of the squid that this is located at the surface of the fiber and practically none in the axoplasm (Nachmansohn and Steinbach, 1942). The concentration at the synaptic region is perhaps even higher, presumably by surface condensation on the arborizations (Marnay and Nachmansohn, 1933). The acetylcholine must be protected against it in some manner which is not clear (Dale and Dudley, 1929). Nachmansohn and Rothenberg, 1944, suggest that the choline ester is formed by nerve stimulation, and then renders the cell membrane permeable to ions, depolarizing it and generating a current which stimulates the adjacent region, and so propagates the ester formation and stimulation. The concentration of the esterase in the neural surface is sufficient to provide the needed speed of action even for the central nervous system (Fulton and Nachmansohn, 1943). Nerve axons have a high choline-acetylating activity, indicating that this is concerned in conduction along the axon as well as in the synapse (Nachmansohn, John and Berman, 1946).

Beutner and Barnes, 1945, find that aqueous acetylcholine solutions in contact with cholesterol establish a negative phase-boundary potential and suggest that this could furnish an explanation of negative variation ih living nerve. Triglyceride oils do not give a potential witn acetylcholine, but do with sympathomimetic drugs and would explain sympathetic stimulation. They can be sensitized to acetylcholine by lower fatty acids (T. C. Barnes and Beutner, 1945).

Di-isopropyl fluorophosphate (DFP) destroys choline esterase (A. Mazur and Bodansky, 1946), and so produces effects equivalent to persistent parasympathetic stimulation; those on the eye are useful in *chronic glaucoma* by instillation of 0.05 to 0.2 per cent in oil (see Index).

Sympathetic Neurohormone.—Stimulation of the postganglionic sympathetic innervation of an organ (*f. i.*, the accelerators of the heart or the splanchnics of the intestine) results in the production of a specific sympathomimetic stimulant, so that the perfusate produces sympathetic responses in other organs. With intact animals, these pass into the blood stream, and can be demonstrated on the denervated heart, the salivary glands, the nictitating membrane of the cat, etc.; also by crossed circulation experiments. The sympathetic synaptic transmission therefore also involves the appearance of a mediating substance, which was termed "sympathin" by Cannon, 1931. The substance has not been isolated, but from its pharmacological reactions and its chemical behavior, it is closely related to epinephrine, and is presumably epinephrine itself. It agrees in its sympathomimetic specificity, its easy destruction by oxidants and its sensitization by antioxidants, by denervation and by cocaine. In analogy with acetylcholine, its action is intracellular; for it acts not only after nerve degeneration, but also on tissues which have never been innervated: the amniotic membrane of the chick, the heart of early chick embryos (after the fifth day; also acetylcholine; Markowitz, 1931), and tissue cultures of embryonic chick heart. Minor differences, which have been described, appear insignificant (Bacq, 1934).

ME and MI Sympathins.—To account for the sympathetic response being excitant in some organs and inhibitory in others, Cannon and Rosenblueth, 1933, suggested that the sympathin (or epinephrine) does not act directly, but constitutes an intermediary substance "M," which then combines in the cells with a postulated excitant precursor "E" or inhibitant precursor "I" to form the assumed compounds "ME" = "sympathin E," or "MI" = "Sympathin I," which would constitute the effective substances that pass into the blood. The arguments for differentiation of sympathin and epinephrine are reviewed by A. Rosenblueth, 1937. It has been suggested (Bacq, 1937; Greer *et al.*, 1938) that "ME" is demethylated epinephrine (*nor-adrenaline;* arterenol). Oxidation of epinephrine by phenolase *in vitro* forms inactive *adrenochrome,* and then *adrenoxine,* which is inhibitory (review, Jeanne Lévy, 1940) and is supposed to constitute "MI." It is further assumed that this oxidation takes place in the cells inhibited by epinephrine, and not in those that are augmented, thus explaining *why some organs are excited, others inhibited* and others diphasic. *Sympatholytic drugs* are supposed to accelerate the oxidation. However, the actual occurrence of these processes in the cells is lacking in convincing experimental support; on the contrary, the perfusate or blood stream from an inhibited organ never produces inhibitory responses in an organ which is normally excited by sympathetic stimulation, or *vice versa,* as the hypothesis seems to demand. On the other hand, the chronaxia is lengthened both in inhibitory and in augmentory responses to sympathetic stimulation and to epinephrine (Florkin, 1929), so that the basis of the action appears identical in both cases, although the mechanical response is different.

Stimulation of the cardiac sympathetic trunk in frogs perfused with saline solution liberates *calcium ions* from the heart (A. Lanczos, 1936).

Epinephrine as an Oxidation-Reduction System.—The rapid oxidation of epinephrine in the blood and tissue results in physiologically inactive end products. It is a natural assumption that these may again be deoxidized to active epinephrine by the sympathetic nerve impulse, thus furnishing a rotating oxidation-reduction system analogous to the hydrolysis-esterification of acetylcholine in the parasympathetic system; but this has not been demonstrated.

It does not follow that the epinephrine acts on the cell through its oxidation-reduction potential, which is the same for both the optical isomers, while the action is much greater for the levo- than for the dextrorotatory epinephrine. *In vitro,* oxidation of epinephrine occurs in the side chain, yielding geno-adrenaline and adrenalone, or in one of the two phenolic hydroxyls, giving a "quinoid." This is devoid of sympathomimetic action, but recovers it by reduction. Adrenalone has only $\frac{1}{200}$ to $\frac{1}{300}$ the activity of epinephrine (Tiffeneau, 1934). Intravenous injection of sodium *permanganate* (10 to 20 mg. per Kg.) persists for a short time in the blood, and by oxidation prevents response to intravenous injection of epinephrine, but not to electric stimulation of the sympathetic nerves, presumably because it reaches the store of epinephrine in the nerve endings (Bacq, 1938).

Sensitization by Denervation.—The sensitiveness of an organ to epinephrine increases materially after degeneration of the postganglionic fibers following excision (Meltzer and Auer, 1904). This is especially marked for the augmentory responses. It can also be demonstrated for parasympathetic reactions (S. C. Shen and Cannon, 1936). The sensitization does not occur immediately after excision, so that it is not due to removal of central inhibition. It develops with the degeneration of the severed nerve fibers and reaches its maximum about the fifth day. Degeneration of the preganglionic fibers does not sensitize, or only to a slight degree (Elliott, 1905; Cannon and Rosenblueth, 1936). Results of H. G. Wolff and Cattell, 1937, indicate that the sensitization is due to the accumulation of effector substance (epinephrine), which is normally used up by the sustained bombardment of the nerve impulses from the ganglion cells.

Lissák, 1938, found that denervated superior cervical ganglia give extracts with epinephrine action, instead of the normal acetylcholine. After degeneration following removal of one superior cervical ganglion, the iris of this side is more sensitive to atropine as well as to epinephrine; pilocarpine and acetylcholine also become mydriatic on this side, the response to ephedrine and cocaine is diminished, and that to amphetamine is unchanged in cats (M. E. Drake *et al.*, 1939). Cutting merely the preganglionic nerve causes this iris to respond less strongly to mydriatic and more strongly to miotic drugs (Lanczos, 1939). Excision of the superior cervical ganglion augments the response of the *submaxillary gland* to pilocarpine and acetylcholine, as well as to epinephrine (Simeone and Maes, 1939). Denervation of *intestines* sensitizes to epinephrine, not to ephedrine or cocaine (Drake *et al.*, 1939). Denervation of the skeletal *rectus muscle* of toads sensitizes them to acetylcholine and to nicotine contracture. This has been attributed to decreased potassium content. Soaking in calcium solution has the opposite effect (L. Y. Lee, 1939).

Cocaine Sensitization to Sympathetic Stimulation.—Froehlich and Loewi, 1910, discovered that intravenous injection of cocaine (which has little effect on the spontaneous autonomic activity even after postganglionic degeneration) materially increases the responses of the blood pressure, iris and urinary bladder to epinephrine. This has been confirmed for the other responses of epinephrine, including the hyperglycemia, but is less marked for inhibitory than for augmentory reactions. The sensitization extends also to electrical stimulation of the sympathetic nerves (Rosenblueth and Rioch, 1933), but the sensitization to epinephrine is even greater after degeneration of the postganglionic fibers, the two sensitizations being additive (Rosenblueth and Cannon, 1932). The denervated nictitating membrane of the cat is thus used by Cannon and his associates as a delicate test for epinephrine or "sympathin." Cocaine probably acts by inhibiting the enzyme that oxidizes epinephrine.

Other local anesthetics (or other ecgonine derivatives) do not produce an equivalent sensitization to epinephrine (and desensitization to ephedrine) (Wirt and Tainter, 1932), although there is some such tendency (Bacq and Lefebvre, 1935). The cocaine sensitization is confined to epinephrine and closely related derivatives (Tainter, 1931). The responses to ephedrine and tyramine are more or less inhibited; those to the nonspecific stimulants (posterior pituitary, strophanthus, barium) are not affected (review, Bacq, 1934).

These statements apply chiefly to the blood pressure and to the nictitating membrane of cats. Other organs may differ. In the *intestines* of unanesthetized dogs (Thiry-Vella loops), epinephrine, tyramine and ephedrine decrease the tonus and amplitude; cocaine, intramuscularly, abolishes the depressive response to tyramine and ephedrine and has little effect on that of epinephrine (C. M. Gruber, 1936). In perfused frog legs, cocaine and most local anesthetics (but not procaine) abolish the vasocontrictor response to barium, while the response to epinephrine remains active (Rentz, 1930).

The destruction of epinephrine by perfusion through the leg of cats is decreased by the addition of cocaine, ephedrine or tyramine (W. S. Lawrence, Morton and Tainter, 1942). *In vitro*, cocaine inhibits the accelerating effect of acetaldehyde on the oxidation of epinephrine by potato *tyrosinase*, while this is accelerated by ergotamine, F 933 and F 833, the substances which desensitize to epinephrine (G. Bayer and Wense, 1938). This suggests a tempting explanation of sensitization and desensitization.

Sympatholytic Action.—Responses to stimulation of the sympathetic nerves or to epinephrine are prevented (paralyzed) by the ergot alkaloids ergotamine and ergotoxine (but not by ergonovine; Cannon and Bacq, 1931), by dibenzyl-beta-chloroethylamine (M. Nickerson and Goodman, 1946), and by yohimbine (Langecker, 1926; Hamet, 1927), synthetic phenoxyethylamine and dioxane derivatives synthesized under Fourneau, J. Lévy and Ditz, 1933, and somewhat by the methyl xanthines (N. Fredericq and Descamps, 1921). The ergot alkaloids have been especially investigated, although they produce a variety of other actions which make the interpretation difficult; and they act chiefly on the augmentory reactions. It has been shown (Navratil, 1927) that the interference is with the motor response, not with the formation of "sympathin" (analogous to the atropine parasympathetic paralysis). Bacq suggests that the ergot desensitization is a result of increased muscular tone, which is known to decrease the response to epinephrine. C. W. Darrow, 1943, also denies true sympatholytic action to the ergot alkaloids and attributes the effects chiefly to parasympathetic or physostigmine-like actions.

Fourneau "F 883," diethylamino-methyl-3-benzodioxane, is both adrenolytic and sympatholytic. "F 933," piperidine-methyl-3-benzodioxane, is adrenolytic, but not sympatholytic. These compounds are not used clinically because of side actions. The Nickerson and Goodman compound, *dibenzamine hydrochloride*, is clinically effective by all routes of administration.

Tokieda, 1927, reported that *ergotoxine* annuls the inhibitory as well as the augmentory effects of epinephrine on the uterus, intestines, blood vessels and excised eyes. It had no effect on the uterine actions of pilocarpine, quinine, hydrastinine and pituitary; it had only slight effects on the cocaine action on the eye and uterus. Tainter, 1932, also found that doses of ergotamine which reverse epinephrine do not alter the pressor response to barium and pitressin, and do increase the response to strophanthin. *Quinine* (0.003 to 0.02 per cent) reverses the augmentory effects of epinephrine on excised organs of rabbits (pregnant uterus, bladder trigone) and has no effect on inhibitory responses to epinephrine, nor on the barium and pilocarpine stimulation (Fujita, 1927). All sympatholytic agents diminish the chronaxia of smooth muscle materially, without affecting that of striped muscle (Lapicque, 1934). Low concentrations of ergotoxine, yohimbine and F 933 sensitize rabbits' ear to epinephrine, but not the frog heart or blood pressure. Higher concentrations antagonize epinephrine and sympathetic stimulation; but with cats' nictitating membrane they abolish only the epinephrine response, not that to stimulation of the sympathetic nerve, which may be increased (C. S. Jang, 1941). *Yohimbine* diminishes or reverses the epinephrine blood pressure rise, but not that of electric sympathetic stimulation or of nicotine or acetylcholine in atropinized animals (Koppanyi, Linegar and Herwick, 1943). Yohimbine does not diminish other epinephrine effects (Hutchinson, Shaw and Wragge, 1942). Benzylimidazoline hydrochloride (*Priscol*) stimulates the ileum, apparently by a cholinergic action, for it is inhibited by atropine or trasentine (Yonkman, Hays *et al.*, 1946). *Ascorbic acid* probably inactivates sympathomimetic amines by deamination. Its administration diminishes the excretion of amphetamine as such (K. H. Beyer, 1941).

Ephedrine, whose chemical structure and pharmacological actions appear, superficially, closely related to those of epinephrine, differs fundamentally in its manner of action; for the effectiveness of ephedrine is not increased, but definitely diminished both by nerve degeneration and by cocaine (Burn and Tainter, 1931). The difference is conditioned on the absence of the phenolic hydroxyl groups (Hamet, 1931), which is also responsible for its resistance to oxidation. The significance of the difference, however, is not clear, especially in view of the striking (but not universal) agreement in their sympathetic stimulation, and the fact that both act after nerve degeneration. *Tyramine* resembles ephedrine.

Dibenzyl-beta-chloroethyl amine and related compounds block and reverse augmentory adrenergic responses. After its administration, epinephrine and other sympathomimetic amines do not raise the blood pressure even with large doses, but instead produce a moderate fall. Inhibitory responses to epinephrine, such as the relaxation of nonpregnant uterus, are not altered. The blocking effect of a single dose may last some four days, although the substance is rapidly destroyed at the *p*H of the body, suggesting destruction of a reacting substance which is but slowly replaced. Eventual recovery is complete. Large doses produce chronic convulsions. Moderate doses protect dogs against cardiac irregularities of epinephrine-cyclopropane. The substance is effective by mouth; hypodermic injection produces local necrosis. It is promptly destroyed by sodium thiosulfate (M. Nickerson and Goodman, 1946).

Limitations of Specificity.—The preceding presentation is schematic and includes chiefly the typical effects, as they are currently conceived. When the doses and other conditions are varied, many of these drugs depart more or less from the schema. There are a number of drugs (for instance, histamine and pituitary extract) which do not fit anywhere in the schema, but whose actions involve isolated functions of one or both divisions.

With some autonomic drugs the response is reversed by altering the dosage; for instance, in the action of pilocarpine on the vagus. In such cases the critical concentration generally varies for different organs, so that a certain dosage may stimulate the innervation of one organ and depress that of another. Modifications in the excitability of an organ, for instance by the presence of other drugs, may alter its response. It is also suggestive that perverted drug specificity is most prominent in organs in which the innervation is itself unusual or confused. It is especially common when the tissue receives only one innervation, or when one innervation predominates largely over the other, or where both systems produce the same response; for instance, in the sweat glands, the genito-urinary system, the frog's lungs, the blood vessels

Optical Isomers.—Most if not all autonomic poisons are optically active (or racemic); and the chemic reactions which determine their specificity depend largely on their stereochemic configuration.

Our knowledge of these phenomena dates from the classic discovery of Pasteur that racemic tartaric acid is separated into its optical constituents by mold fungi. Since then, numerous instances have been worked out on higher animals; such as atropine and hyoscyamine; atroscine and scopolamine; the epinephrines, muscarines, nicotines, cocaines, cinchona alkaloids, camphors, etc. Cells and ferments distinguish sharply between these stereoisomers, so that they differ, at least quantitatively, in their pharmacologic effects, the racemic being intermediate between the active forms. In higher animals, the l-alkaloids usually have more powerful peripheral effects. It is probable that the cells can either attack or destroy the one isomer more readily than the other (Poulsson, 1910). With nicotine, both isomers are equally toxic for protozoa and arthropods, but for annelids, chaetognatha and vertebrates the levo is more potent than the dextro. It may therefore be assumed that the receptive substance is optically active in these, and not in the lower forms; and this is probably connected with the appearance of acetylcholine in the nerve transmission (Gause and Smaragdova, 1939). The asymmetric nitrogen atom also modifies the pharmacologic actions, as shown by Hildebrandt, 1905, for conines, and Laidlaw, 1913, for canadines. The curare action of the ammonium bases (Brown and Fraser, 1869) depends upon the peculiar orientation of the pentavalent atom of nitrogen or similar elements "The Biological Relations of Optically Isomeric Substances" forms the subject of a monograph by A. R Cushny, 1926 (Williams and Wilkins Co.).

Synergistic Phenomena.—When autonomic tissues are exposed simultaneously to several autonomic drugs that act in the same direction, the resultant effect is more or less additive, constituting *synergism*. The degree of summation is less complete if the drugs act on the same system (because of the Weber-Fechner law of diminishing returns) than when they act on different systems or structures. The latter constitutes *supplementary synergism;* the former, *complementary*. This principle is helpful in locating the site of action. *Potentiated synergism* exists if the resultant response is materially greater than the addition product of the two separate actions, especially if one of the agents has little or no action effect when used alone. Instances are the *sensitization* of physostigmine for acetylcholine, due to diminished destruction; and the sensitization of cocaine for epinephrine, probably due to a similar cause; but other mechanisms may be involved, as in the sensitization of the uterus in the course of pregnancy.

Antagonism exists if the two agents act in opposite directions. It tends to result in mutual neutralization, or in algebraic summation, which is generally more or less skewed. The most peripheral actions would tend to predominate over those exerted more centrally; accordingly the ganglionic effects are obscured by the actions on the responsive cells. If two drugs are mutually antagonistic, they must both act at the same level. Drugs with opposite actions on the same receptive mechanism (for instance, the parasympathetic) are generally mutual antagonists; but there may also be mutual antagonism between sympathetic and parasympathetic drugs, and between these and the drugs that act on the responsive mechanism. Mutual antagonism is rarely a simple summation; the presence of one autonomic poison modifies the effects of the others, in degree and sometimes in direction. If concentrations of two drugs that produced equivalent effects in opposite directions are mixed, the effect of one usually predominates decidedly over that of the other; for instance, a small dosage of atropine suffices to remove a strong pilocarpine stimulation (Magnus). Again, if a combination has been worked out that is essentially neutral, multiples of this combination are generally not neutral; although in some cases they may be so, within limits (Cushny, 1915). In the pilocarpine-atropine antagonism, pilocarpine action increases with the concentration, atropine with the absolute quantity (Van Lidth de Jeude, 1918). It may also happen that increased excitability produced by one drug renders effective actions of the second drug that are too weak to influence cells of normal excitability, and in this manner the site of action of the second drug may appear to be altered and reversed.

Altered Susceptibility.—Many conditions modify the response of smooth muscle to autonomic drugs, generally quantitatively, but sometimes qualitatively. The more important modifying agents are those with high surface affinity, precipitants, certain lipoids, colloids, changes in Ca, K and H ion ratio (Thienes, 1926).

Clinical Vagotonia and Sympathotonia.—Eppinger and Hess, 1909 and 1910, classified patients into these two groups according to their response to test doses of epinephrine, ergotamine, atropine and physostigmine. Further experience showed that abnormal sensitivity generally involves both autonomic divisions. The various criteria are listed by M. A. Wenger, 1941.

The ion ratio of Ca, K and H ions alters many autonomic functions, quantitatively and sometimes qualitatively. The effects vary for different organs and drugs. Zondek, 1927 ("Die Elektrolyte," Springer, Berlin), generalized from observations on excised heart, stomach, bladder and uterus, that increase of the ratio $\frac{Ca}{K}$ acts like orthosympathetic, and increase of $\frac{K}{Ca}$ like parasympathetic stimulation. Such generalizations are convenient, but the subject is more complicated and there are many exceptions (Bacq, 1934). With excised intestines, for instance, both increase and withdrawal of K augment the tonus and contractions (A. J. Clark, 1921). Lowering of the *Ca level* of the blood or perfusion fluid (in dogs, rabbits or frogs) lowers the excitability of both the sympathetic and parasympathetic division (Bouckaert, 1929). Lowering the $\frac{Ca}{N}$ ratio by increase of Na as well as by decrease of Ca lowers various sympathetic responses (Gley, 1928). The vasoconstrictor response of the perfused ear of rabbits by *epinephrine* requires the presence of Ca, not K, while constriction by ephedrine requires K and not Ca (Pinter-Kovats, 1928). K has directly opposite effects on the epinephrine response in many tissues (Knoefel and Alles, 1938, contradicting Camps and Higgins).

Flocculating agents, including colloids and metallic salts, alter drug responses materially; for instance, Thienes, 1926, found the augmentory response of epinephrine on excised uterus of rabbits increased by soap, camphor, saponin, acacia, tannic acid, paraphenylendiamine; it was reversed by procaine. The barium contracture was increased by saponin, acacia, copper sulfate, paraphenylendiamine and salicylic acid. Van Leeuwen and Györgyi, 1922, reported quantitative changes produced by cephalin and lecithin on the response of excised intestines to pilocarpine and histamine.

Penetration.—The presence of one drug may so alter the penetration or the distribution of the second drug as to modify its effects, without exerting antagonistic actions in the ordinary sense. This was demonstrated by Ehrlich for certain dyes; and similar conditions have been shown by Straub to prevail for muscarine and atropine; and for morphine and chloroform by Fuenher. Asher and Gannus, 1911, found that the gland cells of the nictitating membrane of frogs take up much more of vital stains when they are stimulated by pilocarpine than when depressed by atropine.

The method of administration may modify the distribution of a drug so as to affect the nature of the response, as with intra-arterial injection of choline esters, epinephrine and benzedrine in man (Myerson *et al.*, 1928).

Concentration Gradient.—Drug effects generally diminish when the poisoned solution is washed out, but in some cases the washing at first increases the effect. This has been reported for the action of muscarine on the frog heart (W. Straub, 1907); muscarine, pilocarpine and arecoline on bronchial muscle (Trendelenburg, 1912); intestines and uterus (Kuyer and Wijsenbeek, 1913). Straub assumed that in these instances the effect is due to the *passage* of the agent through the cell membrane either into or out of the cell. It may be questioned, however, whether the phenomena attributed to "*potential gradient*" may not have some clearer explanation (O. Loewi, 1912). For instance, Jendrasik and Moser, 1924, invoked the gradient to explain the observation that the inhibitory action of epinephrine on excised intestines of rabbits passes off during the immersion, long before the significant quantity of the drug has been destroyed; but Gautrelet and Bargy, 1927, showed that the intestine fails to respond also to increase of epinephrine.

Polyphasic Reactions.—Many drugs appear to have several successive and contradictory actions on a given structure, such as the successive stimulation and depression of ganglia by nicotine. This is often due to gradual rise of the concentration as the drug penetrates, or to several really distinct actions that develop with different speed; for instance, the active shortening of a muscle, which must be brief, and the maintenance of tonus, which may be prolonged (Winton, 1930; Clark, 1926; Nanda, 1931). Jendrasik attempted to explain practically all polyphasic reaction by the Straub concentration gradient; but Rentz, 1929, pointed out that this does not apply.

Central Autonomic Control.—The autonomic functions can be carried on independently of the central nervous system, and are not greatly disturbed by denervation. Cats remain in good health and with almost normal functions after complete removal of their sympathetic ganglion chains (Cannon, Newton *et al.*, 1929). Normally, however, the autonomic activities are guided to varying degrees by the nerve centers with which they are connected, from the hemispheres to the cord, but chiefly in the medulla and diencephalon, the centers being "regions" rather than circumscribed locations (review, A. Kantz, 1936). The *medulla* controls especially the vasomotor reactions. The injection of cholinergic drugs and of pituitrin in the lateral ventricles of the brain produces marked parasympathetic stimulation, by excitation of the *hypothalamic centers* in front of the optic chiasm. Stimulation somewhat posterior to this excites sympathetic responses. The motor area of the cerebral cortex also responds to acetylcholine and physostigmine.

Parasympathetic Stimulation from the Lateral Ventricles.—Harvey Cushing, 1931, observed that the introduction of *pituitrin* into the lateral ventricles produces marked vasodilatation, sweating, lacrimation, salivation, vomiting and fall of temperature. *Pilocarpine* produces similar effects in doses which would be ineffective hypodermically. The effect is arrested by atropine, injected either into the ventricles, or hypodermically. The parasympathetic stimulation does not occur in avertin narcosis, presumably because the centers are depressed. In dogs, however, Aird and Montgomery, 1936, found that the salivation response to the ventricular injection of pilocarpine occurred peripherally, after absorption from the ventricles, for it was not affected by extirpation of the parasympathetic nerve supply of the gland. It is conceivable that the centers were too much depressed in their experiments.

The injection of *acetylcholine* and of *physostigmine* into human cerebral ventricles results in characteristic and prolonged reactions by direct action on the centers (W. R. Henderson and Wilson). Intraventricular injection of 0.1 to 0.5 γ of acetylcholine produces prolonged sleep, disturbed respiration and cardiac irregularities similar to vagus stimulation, but no fall of blood pressure. These effects differ materially from the peripheral effects of acetylcholine and are not prevented by atropine. Similar effects are produced by intraventricular injection of nicotine or caffeine, or by clamping both carotid arteries (Dikshit, 1934). *Electric stimulation of the preoptic region* in cats causes contraction of the urinary bladder, slowing of the heart, fall of blood pressure and stimulation of respiration. Faradic stimulation *behind the optic chiasm* results in sympathetic reactions, viz., mydriasis, rise of blood pressure, increased rate and depth of respiration (Ranson, Kabat and Magoun, 1934). H. B. Carlson *et al.*, 1940, describe sympathetic stimulation and parasympathetic inhibition by electric stimulation of the hypothalamus. ("Psychosomatic Medicine" of January, 1939, contains reviews of the hypothalamus, with extensive bibliographies.)

Removal of the cerebral hemispheres in the higher vertebrates is followed by increased activity of certain viscera with autonomic control, such as the heart and intestines. Administration of mecholyl to patients with *frontal lobe lesions* produced sympathetic stimulation contralateral to the lesion (S. M. Fisher and Stavraky, 1944). In monkeys, *stimulation of the premotor area* causes vigorous intestinal peristalsis (Fulton, Kennard and Watts, 1934). Gastric movements in the monkeys were not augmented by faradic stimulation of the cortex, but inhibitory effects were obtained by stimulation of the frontal and premotor areas (D. Sheehan, 1934). Chatfield and Dempsey, 1942, describe characteristic changes in the somesthetic, motor and auditory areas rather than spontaneous activity.

The cerebral motor cortex of cats also responds with specifically localized *somatic movements* to the local application of physostigmine; *i. e.*, contralateral tremor, rigidity and clonus of the same muscles that respond to the electric stimulation area (F. R. Miller, 1937). *Electroencephalograms* show increased activity on application of *physostigmine* or *acetylcholine* to the motor cortex with potentiation of the two drugs. Cerebral application of *atropine* modifies these effects (Miller *et al.*, 1938). The acetylcholine discharges are preceded by depression of the electrical activity (F. M. Foster *et al.*, 1946). Epinephrine has no effect when applied alone, but the response to acetylcholine is materially augmented by low concentrations and depressed by high (review, J. H. Burn, 1945).

Local application of acetylcholine to *the floor of the fourth ventricle* produces hyperactivity of the respiratory center, with potentiation by physostigmine (Gesell, Hansen and Worzniak, 1943). In man, intrathecal *spinal injection* of acetylcholine has little effect. Physostigmine produces transient depression of the spinal reflexes, followed rapidly by increased excitability. Prostigmine depresses the muscular tonus and reflexes, without change of sensation (M. Kremer, 1942).

The exclusive role of acetylcholine synaptic transmission in the central nervous system is neither proved nor disproved. It appears inherently improbable, especially because of the rapid sequence of reversals in tetanus. These difficulties are perhaps removed by the high concentration of choline acetylase in the reacting surface, and by the reversibility of its action. W. Feldberg, 1945, considers the evidence good for some central synapses, but not for others.

AUTONOMIC REACTIONS OF THE GASTRO-INTESTINAL TRACT

Innervation.—The entire gastro-intestinal canal is innervated from both autonomic systems. The orthosympathetic supply comes through the splanchnic and mesenteric ganglia. The parasympathetic supply from the esophagus to the ileum is furnished by the vagus; the erigens and pelvic innervate from the colon to the anus. The functions of the two systems are reciprocally antagonistic. Parasympathetic stimulation generally augments the contractions or tone of both coats of the muscular tube; orthosympathetic stimulation augments the sphincter tone and inhibits the muscular tube. This reversed arrangement of the orthosympathetic innervation of the sphincters and the muscular tube simplifies their functional cooperation. The intrinsic functions of the intestinal musculature, especially its tonus, play an important part in their behavior, and may profoundly modify their reactions to nerve stimulation and to drugs. Consequently there are conspicuous exceptions to the simplified schema in some situations, which vary, not only with different species, but even in the individual animal, at different times. The small intestines of mammals, however, respond generally by augmentation to parasympathetic stimulation and by inhibition to orthosympathetic stimulation.

Innervation of the Sphincters.—According to Gaskell, the orthosympathetic appears to augment the tonus of most if not all sphincters; in the urinary as well as in the digestive tract. Parasympathetic stimulation inhibits the urinary sphincters and the internal sphincter ani; but the response on other sphincters has not been definitely established. The cardial sphincter may respond by either augmentation or inhibition, to either vagus or sympathetic stimulation (Carlson, Boyd and Pearce, 1922).

Visceral pain arises if the excitation is extreme, and from moderate stimulation of certain kinds, especially by stretching; but it is not clear whether this acts directly or by causing ischemia, for vascular spasm or occlusion also gives rise to severe pain. The pain-excitability may be increased by rise of temperature or by chemicals, especially by toxins.

The Significance of the Intestinal Nerve Plexuses.—There is no good reason to assume that the ganglionic nerve plexuses of Auerbach and Meissner differ in function from the analogous ganglionic plexuses in most autonomic organs, for instance the heart, or to doubt that they are the neuron cells of the efferent link of the parasympathetic nerves (Gaskell).

They have, however, also been interpreted as peculiar peripheral nerve centers, the "*enteric system*" of Langley (1900, 1913) for the local coordination of peristaltic reflexes. According to this view they might be excited and inhibited by afferent impulses directly from the intestinal mucous membrane and muscle, as well as by efferent impulses from the central nervous system. This explanation was suggested by the impressive appearance of the nerve plexus and the apparent complexity of intestinal coordination; it seemed to be supported by the observation of Magnus (1904), that the removal of the nerve plexus suppresses the rhythm of intestinal strips. It was subsequently shown, however, that the plexus-free strips remain rhythmic if proper precaution is taken to prevent injury of the muscles, and that coordinated peristaltic movements can be evoked in muscle that has been kept on ice five days, when nervous structures would presumably have died (Gunn and Underhill, 1914, 1916; Alvarez and Mahoney, 1922). The myenteric plexus has a high resistance to anoxia; this may be connected with its high acetylcholine content (J. H. Welsh and Hyde, 1944). This leaves no direct evidence for the local coordinating centers.

The progression and coordination of peristalsis can be adequately explained by the inherent properties of smooth muscle, especially the gradient of tonus and the stimulant effects of distention. The electric potential changes accompanying intestinal movements indicate that these are syncytial, with conduction impulses within the muscle (E. Bozler, 1939). It may be recalled that the uterus executes equally complex movements without needing an enteric system.

The Intestinal Movements.—The intestines, like the uterus and ureter, exhibit two fundamental types of movement: (*a*) pendulum rhythm; (*b*) localized contraction rings, stationary or progressive, *i. e.*, peristaltic. Both types are modified by the prevailing state of tonus and excitability, local and general, of the intestinal muscle. For the whole small intestines, there is a strong general gradient of tonus, decreasing from the pylorus to the cecum, which determines the descending direction of the peristalsis. In the large intestine, the gradient varies from time to time, and this determines peristalsis and antiperistalsis.

Pendulum movements consist of continuous rhythmic contractions of the longitudinal muscle of the "resting" intestines, at the rate of about ten per minute. They are conspicuous through their regularity and from the fact that they are well maintained by the excised intestines immersed in oxygenated Ringer's solution (Magnus, 1904) and are therefore easily studied. They have no material effect, however, on the intestinal lumen, and do not have any apparent function; they are perhaps a mere by-play of the healthy excitability of the intestinal muscle. They are diminished or arrested if the general excitability of the intestine is low and when the contraction of the strong circular muscles interferes with the movements of the weaker longitudinal coat. Pendulum movements of the circular muscles, on the other hand, if they exist, are so much more feeble than those of the longitudinal muscle that they are not ordinarily observable.

Differences of Rhythm at Various Levels.—In intact animals, the rhythm is faster toward the ends of the intestine than toward the middle. In excised intestine, the rate decreases with the distance from the pylorus; the rate of the duodenum in rabbits is about 50 per cent faster than in the lower ileum. The oral end is more irritable and therefore acts as pacemaker. It is also less subject to epinephrine relaxation and its tone is higher. The slower rate of the aboral end is accompanied by greater excursions (Alvarez, 1914, 1915). The different rates are perhaps based on intrinsic differences in the intensity of metabolism. Cyanide, or shutting off the oxygen supply, interferes more with segments from the higher portions of the intestine. Alvarez and Starkweather, 1918, believe that this gradient of excitability is mainly concerned in regulating the physiologic rate of propulsion of the food through the various levels of the intestinal tract.

Drugs on Intestinal Rhythm.—The effects have been studied by Alvarez, 1918. The changes in rhythm are not necessarily parallel to those of the tonus and amplitude of the contractions. This has also been found by Pilcher for the uterus.

The peristaltic movements consist of more powerful contractions of the circular coat, which are normally initiated by distention of the intestines, in excised intestines as well as in the living animal (Trendelenburg, 1917). Such distention results first in gradual increase of tonus. When this reaches a critical point, which varies with conditions, the circular coat suddenly contracts, stretches the longitudinal coat, constricts the lumen and expels the contents. The peristaltic contraction occurs only when the intestine is in good condition and tonus, and begins at the region of highest tonus at the oral end of the segment. The contents are propelled in the direction of the lower tonus, *i. e.*, to the adjacent lower segment, which is thereby stretched, distended and thrown into a peristaltic contraction. This accounts for the Bayliss-Starling (1899) "Law of the Intestines" (Alvarez and Starkweather, 1918). The peristaltic wave may travel in this manner, by a purely muscular mechanism, until so much of the contents has been lost on the way that the intestine is not sufficiently distended, or until a region of low irritability is reached. When a segment has contracted, it gradually relaxes, so that it again becomes filled with fluid from above, and the process is repeated, at the rate of two to four contractions per·minute. When normal intestines become empty, peristalsis ceases and a period of rest ensues. If the propulsion of the contents is prevented by an obstruction, functional or mechanical, the contractions increase in violence; but they are rather rapidly fatigued by the excessive pressure. The occurrence and extent of the peristaltic contractions depend on the irritability. When this is high, they may occur even in the empty intestines. The height of irritability is also the chief factor in the extent of spread of the peristaltic wave; exceptionally, a single wave may thus travel rapidly through long disdistances, the so-called "rolling movement" or "peristaltic rush" (*cf.* Meltzer and Auer, 1907). In the large intestine, the gradient of irritability and tonus changes from time to time, so that peristalsis travels in both directions, at different periods.

Stationary Tonus Rings and Intestinal Spasm.—Contractions of the circular coat may also occur without spreading. The specialized kneading "segmentation movements" of the small intestine of the cat are rhythmic contractions of alternating segments. More common are strictly localized contraction rings which persist for long periods sometimes quite stationary, sometimes traveling slowly, and sometimes rapidly. The latter constitute a gradual transition to ordinary peristalsis. These rings may be narrow or wide bands, or extend over a considerable distance, in which case they merge into intestinal spasm. While they persist, they occlude the lumen and form a strong functional sphincter. They constitute the normal type of contraction in the large intestine (Lenz, 1924; Cannon, 1911). In the small intestine they occur only when the irritability is abnormally heightened, especially by the parasympathetic and "muscular" stimulants. They give rise to temporary obstruction, and provoke the phenomena of "colic."

Paresis of the Intestine.—The tonus and excitability of the intestines are sensitive to nervous and chemical conditions, and are easily depressed below the level necessary for the contractions, especially of the circular coat. Temporary inhibitions are perhaps a normal provision for resting the intestines; both temporary and more lasting inhibitions occur clinically, in psychic states, in laparotomies, in intestinal obstruction, etc. *Increased excitability of the muscle* is probably an important factor in the action of many cathartics, especially those that act on the large intestines.

Drug reactions of small intestines are relatively simple: Ordinarily, epinephrine is inhibitory; the parasymptahetic stimulants augmentory; and the nonspecialized drugs produce their usual effects. The longitudinal and circular muscles act in the same direction; but when the circular coat is active, its contraction stretches the weaker longitudinal muscle (Inoue, 1923). Antagonism appears to occur generally between augmentors and relaxors, no matter on which system they act.

Parasympathetic Drugs. — Physostigmine, pilocarpine, choline and muscarine increase the tonus, the pendulum movement and the peristalsis in mammalian intestine. Excessive concentrations produce tonus bands and intestinal spasm. The effects are removed by atropine. This is especially effective against pilocarpine, which is neutralized by doses of atropine much smaller ($\frac{1}{500}$) than those that affect the unpoisoned intestines or block stimulation through the vagus nerve, or by physostigmine (Magnus, 1904).

Pilocarpine.—Neukirch, 1912, found that the action of pilocarpine on the excised intestine is purely stimulant, even with 5000 times the effective dose. The action can be removed by washing, but during the passage of the pilocarpine out of the cells there seems to be a supplementary stimulation.

Pilocarpine-Atropine Ratio.—The antagonism of these drugs on the excised intestine is not in simple ratio to their concentration; for while the pilocarpine, physostigmine and muscarine stimulations depend on the concentration of the drug in the fluid, the atropine inhibition depends on the absolute dosage. The antagonism is not materially influenced by temperature or H ion concentration (van Lidth de Jeude, 1918).

Atropine and Choline.—The effect of atropine on the unpoisoned intestine is variable and inconstant, especially in the excised intestine. This has been attributed to variations in the content of choline that is normally present in the intestinal wall and acts as a peristaltic stimulus: the greater this stimulation, the more pronounced is the sedative action of atropine; when the parasympathetic stimulation of choline is absent, atropine becomes ineffective except in abnormal concentrations (Le Heux, 1918).

Propulsion of charcoal in small intestine in unanesthetized dogs is increased by intramuscular administration of prostigmine (averaging 38 per cent) and ergotamine (27 per cent); it is decreased by atropine (36 per cent) and ephedrine (35 per cent). Cocaine has no appreciable effect (Van Liere *et al.*, 1944).

Epinephrine inhibits the normal intestinal movements, and antagonizes the stimulant effects of pilocarpine, nicotine and strophanthin (Magnus), and also those of barium (Roth).

Nicotine paralyzes the ganglia and therefore renders stimulation of the vagus and of the splanchnic ineffective. At the same time, it produces violent peristalsis and intestinal spasm (Nasse). This stimulation is the most conspicuous effect in excised intestine. It may be preceded by brief inhibition, and with large doses it is followed by paralysis (Trendelenburg, 1917; Magnus, 1904). This paralysis (which is also produced by coniine, curare and gelseminine) is mutually antagonistic with physostigmine stimulation (Ikeda, 1916).

Muscular stimulants include barium, veratrine, colchicine, strophanthin, pituitary histamine, peptone and anaphylaxis. They produce violent stimulation, increase of tonus and intestinal spasm. Their antagonisms follow the usual pattern: They are effectively relaxed by the muscular depressants, including the nitrites and magnesium. They are also relaxed by sympathetic stimulation through epinephrine; but parasympathetic paralysis, by atropine, has little effect (Magnus, 1904; Roth, 1923; Sollmann and Rademaekers, 1925). *Morphine* produces a peculiar increase of tonus which does not proceed to spasm, but prevents peristalsis.

Histamine, peptone and pituitary extract act less definitely on the intestines than on the uterus. In general, they produce more or less stimulation, which tends to be followed by relaxation. Pituitrin generally gives initial stimulation followed by inhibition (Krishnan, 1934). The details vary in different animals (Olivcrona, 1921), and appear to be somewhat influenced by diet (Degener, 1922). Various *amino acids* have practically no effect (Hirschfelder and Cantwell, 1918). *Anaphylaxis* produces marked stimulation; normal *serum* also tends to stimulate, but the response is uncertain (Schlecht and Weiland, 1921). *Colloids* often enhance the reaction to other stimulants. Van Leeuwen and Szent Györgyi, 1922, studied the influence of cephalin and lecithin on the response to pilocarpine and histamine.

Muscular Depressants.—The intestines are relaxed and inhibited by magnesium, nitrites, chelidonine, papaverine (not narcotine), the benzyl esters (Trendelenburg, 1917). *Insulin* stimulates the intestinal movements indirectly by lowering the blood sugar level (Krishnan, 1934). Its direct action on excised intestines is depressant (Farah, 1938).

"Female Remedies" on Excised Intestines.—Delzell, Burman and Pilcher, 1916, found the effects on rabbit's intestine practically the same as on the guinea pig uterus. Caulophyllum, however, leaves the tonus almost unchanged, while the amplitude is lowered. Valerian (oil) depresses the contractions. The viburnums are inactive.

Hydrogen Peroxide.—Very weak concentrations (sometimes 1:1,000,000) increase the tonus of excised intestine temporarily; this soon returns to normal and further peroxide is then ineffective. Larger doses inhibit the movements (H. J. Hamburger and Brouwer).

The Oddi sphincter is reported to be spasmodically contracted in man by the presence of dilute hydrochloric acid in the duodenum and by administration of morphine. Atropine relieves the spasm induced by acid, but not that of morphine. Duodenal instillation of magnesium sulfate solution relaxes the sphincter, papaverine produces brief relaxation, and epinephrine has little effect (Doubilet and Colp, 1937). W. Walter *et* al., 1937, observed little change with parasympathetic stimulants, atropine, ergotamine, alcohol, histamine, adenosine phosphate and papaverine.

Reactions of the Large Intestine.—The normal movements are generally more sluggish than those of the small intestines (Alvarez and Starkweather, 1918), and persistent tonus bands are especially important (Cannon, 1911). Their reactions to the autonomic drugs agree generally with those of the small intestines (Lenz). They respond more readily to the emodin irritants (senna, rhubarb, etc.).

The ileocolic sphincter is closed by stimulation of the splanchnic nerve; it does not appear to have an inhibitory innervation. It is contracted by epinephrine (Elliott, 1904). Kuroda, 1916, and H. Schroeder, 1933, reported that it is also contracted by pilocarpine and that this is antagonized by atropine. Morphine caused prolonged contraction; papaverine, relaxation.

The **muscularis mucosa** of the small and large intestines has both cholinergic and adrenergic augmentory innervation. Inhibitory nerves have not been demonstrated. The rhythmic movements are myogenic, but may be augmented by nerve stimulation (C. E. King and Robinson, 1945). The movements of the intestinal villi are increased by vagus stimulation and inhibited by atropine (V. Ludany and Jourdan, 1936).

The **gastric musculature** is generally stimulated by parasympathetic and relaxed by orthosympathetic stimulation. The responses of the fundus and sphincters differ in detail, and are modified by the functional condition of the muscle: Low tonus favors stimulation; high tonus, relaxation. *Parasympathetic stimulation* through the vagus nerve, pilocarpine, cholines, or physostigmine augments the contractions of the fundus if the tonus is low; but the same doses may inhibit the contractions if the tonus is high (M'Crae and MacDonald). Pilocarpine increases the tonus of the pyloric sphincter and hastens its contraction (J. E. Thomas, 1929; H. Schroeder, 1933). In most human subjects, the emptying of the stomach begins earlier, but is completed later (Herrion, 1936). The intragastric pressure is raised. *Atropine* inhibits all the effects of parasympathetic stimulation on the fundus and sphincter. In normal human subjects and dogs it delays both the initial and the final emptying time (Herrion). *Epinephrine or stimulation of the orthosympathetic nerve* generally arrests the rhythmic movements and lowers the tonus of the cardial and pyloric sphincters as well as of the fundus; but if the tonus is already low, they may give slight augmentation. In rabbits it generally stimulates. *Ergotamine* relaxes epinephrine contraction. *Ephedrine* acts similarly to epinephrine. Its gastric effects do not last as long as the blood pressure rise (M'Crae and MacDonald). *Nicotine* depresses and often arrests the movements and lowers the tonus of the excised stomach; but in intact animals it causes violent emesis by central action. *Gastro-intestinal hemorrhages and acute ulcers* may result from the violent contractions induced by large doses of the parasympathetic or muscular stimulants, acetylcholine, pilocarpine, physostigmine, histamine, pitressin (Necheles and Masur, 1939).

The emptying time of the stomach in normal human subjects, measured by intubation, is not materially altered by clinical doses of mecholyl, prostigmine, atropine, ergotamine, amphetamine, trinitrin or sodium bicarbonate. It is delayed by morphine (Folley and Abbott, 1942).

Esophagus.—In dogs and rabbits this consists of striped muscle and reacts as such: Although it is innervated by the vagus, it is inhibited by curare and not by atropine. In man and cat, the lower third consists of smooth muscle, which is inhibited by atropine and not by curare (V. Koenig, 1928).

Pigeon's Crop.—The responses of the pigeon's crop to autonomic drugs were described by Hanzlik and Butt, 1928.

Gastro-Intestinal Reactions of Cold-Blooded Animals.—These do not show pendulum movements, but their tonus waves and rings are similar to those of mammals, though slower. Epinephrine is inhibitory, as in mammals, but parasympathetic stimulants also tend to produce inhibition. This is especially marked in the *small intestine of the frog*, which is relaxed by epinephrine, pilocarpine, physostigmine and nitrites; and each of these is antagonistic to the contractor effect of barium. This is perhaps the most definite instance of inhibitory sympathetic stimulation by the parasympathetic stimulants. It has the further unique peculiarity that it is not antagonized by atropine. The direction of these reactions is not influenced by the ion ratio or H ion concentration of the bath (G. B. Roth, 1923).

Small Intestine of Turtle.—Epinephrine is inhibitory and pilocarpine and barium augmentory, as in mammals; but physostigmine tends to inhibit, and tyramine to stimulate. Atropine relaxes and antagonizes barium as well as pilocarpine, although it is less effective against barium (Roth, 1923).

Rectum of Frog.—The innervation is parasympathetic augmentor and orthosympathetic inhibitory. The excised organ is inhibited by epinephrine and stimulated by the parasympathetic stimulants; the latter are antagonized by atropine. Muscarine, the methyl ammoniums and arecoline stimulate strongly, but pilocarpine only slightly, and physostigmine still less; and pilocarpine actually removes the arecoline stimulation (Schueller, 1921). Similar phenomena have been described for the frog stomach.

The frog's stomach has been an important object for the study of the general properties of smooth muscle. Goltz used it in 1872 to demonstrate the reflex tone and inhibition of the alimentary tract. Bercovitz and Rogers, 1921, investigated the response to nerve stimulation; also in the turtle. The reactions to drugs are described by Fuehner, 1918.

The esophagus of frog is generally inhibited by epinephrine and stimulated by pilocarpine, but it behaves abnormally to the muscle poisons. Barium is said to have no effect, and histamine and pituitary inhibit (Bercovitz, 1922).

The esophagus of turtle appears to show a marked difference in response according to the duration of the application. At first, epinephrine is stimulant, pilocarpine depressant; after a time epinephrine becomes depressant and pilocarpine stimulant. Histamine produces stimulation (Bercovitz, 1922).

The intestine of fly consists of striped muscle, but performs peristaltic movements similar to those of higher animals. Its behavior toward drugs resembles that of smooth rather than striped muscle (T. B. Robertson, 1920).

AUTONOMIC REACTIONS OF THE MUSCULATURE OF THE GENITO-URINARY ORGANS

Uterus.—The innervation of the uterus is essentially orthosympathetic, through the hypogastric nerve. There is also a parasympathetic supply from the pelvic nerve, which appears to act in the same direction (Cushny, 1906, 1910), but so feebly and uncertainly that it is generally considered negligible. The uterus, however, reacts readily to parasympathetic as well as to sympathetic drugs, and most actively to direct muscular stimulants, especially pituitrin, the ergot alkaloids and histamine (review, Gruber, 1933).

Natural Movements of the Uterus.—The excised uterus when placed in oxygenated Ringer's solution executes pendulum and peristaltic movements (Kehrer, 1908; Cushny 1910) which vary in intensity and type with the sexual cycle; the predominance of progesterone renders the uterus less contractile in the course of pregnancy, while increase of estrogenic hormones renders it more contractile and precipitates parturition. Analogous movements occur normally in living animals and may be watched by inserting a permanent celluloid window in the abdominal wall (Ludwig and Lenz, 1923; Tscherepachin, 1928). They may be recorded clinically by a piston resting on the abdominal wall over the parturient uterus (Dodek, 1932; Barlow and Jones), or by a rubber bag inserted into the uterine cavity post partum (Moire). The reactions of the excised uterus are quite similar to those *in situ*, except for drugs that increase the output of epinephrine in living animals (Dale and Laidlaw, 1912). In nongravid animals the peristaltic movements are relatively slight and alternate with pauses, much as in the intestines. Parturition is accomplished by powerful peristaltic waves, producing the labor pains, which are aided by the contraction of the abdominal muscles and diaphragm. The nongravid contractions may be intensified or allayed by central impulses; but normal labor may occur after complete severance of the uterus from the central nervous system (Elkin, 1922).

Clinical Drug Responses of the Parturient Uterus.—The records obtained by Dodek, 1932, with an external hysterograph on women in the successive stages of labor show that the uterine contractions are increased by clinical doses of pituitrin (even small doses produce marked stimulation and incomplete relaxation) and ergonovine, which is very active even by mouth. Ergotoxine intramuscularly was rather unreliable. Epinephrine caused brief arrest of the contractions. Quinine, morphine and scopolamine did not produce any significant effects. *Various anesthesias* react as follows: *Ether* depresses the contractions in proportion to the degree of anesthesia. Ether analgesia, inhalation or rectal, renders them somewhat more shallow, so as to interfere materially with labor. Complete surgical anesthesia with ether abolishes them completely. This would also hold for *chloroform*. *Avertin* (with amylene hydrate), 60 mg. per Kg., depresses more than colonic ether analgesia. *Amytal* sodium sleep (6 to 12 grains) produces practically no depression. *Nitrous oxide with oxygen* does not weaken the contractions, even in deep anesthesia. *Procaine spinal anesthesia* does not alter them significantly.

Effects of pharmacologic reagents on *uterine action potentials* are reported by Bozler, 1931; R. S. Morison, 1940; Balassa and Gurd, 1941.

Sympathetic Stimulation (Epinephrine).—The response varies, in the same direction for *epinephrine* and for hypogastric nerve stimulation, according to the species and the functional state of the uterus. *Human uterus* has two layers of muscle of different embryologic origin and function. The exterior is concerned with expulsion in parturition, and is stimulated by epinephrine; the inner layer is especially strong at the cervix, and its contraction represses expulsion. It is inhibited by epinephrine so that both actions of epinephrine assist parturition (J. Daels, 1941). Epinephrine tends to increase uterine tonus and movements in most species (monkey, dog, rabbit, hedgehog). This stimulation is more marked in pregnancy; but strong or spastic contractions, as in actual labor or by ergot, pituitary or histamine, are generally relaxed by epinephrine. The pregnant cat uterus is also contracted by epinephrine, but the nonpregnant uterus is generally relaxed by it. The change of response is related to the concentration of progesterone (J. H. Kennard, 1937). In the final stage of pregnancy the cat uterus is again inhibited by epinephrine (E. C. Del Pozo, 1946). Guinea pigs, rats and mice usually show relaxation, both when pregnant and nonpregnant (Gunn and Gunn, 1914; Athias, 1921). Guinea pig and rabbit uterus reacts alike (almost quantitatively) toward other drugs (pituitary, ergot, pilocarpine, atropine, quinine, potassium, calcium).

Parasympathetic Drugs.—In animals in which sympathetic stimulation produces contraction, the parasympathetic stimulants also produce contraction (Cushny, 1910). When the sympathetic response is inhibitory, the effects of parasympathetic stimulants are inconstant. Atropine depresses the normal uterus *in situ* (Ludwig and Lenz, 1923) and antagonizes the pilocarpine contraction (not that of hypogastric stimulation).

In nonpregnant cats, in which hypogastric stimulation or epinephrine usually relaxes or inhibits the contractions, Cushny also noted inhibitory phenomena after pilocarpine injection; but they were much less characteristic than with epinephrine. Dale and Laidlaw did not observe relaxation when the excised nonpregnant uterus was subjected to pilocarpine, although it occured sometimes during life. This they attributed partly to increased suprarenal output, partly to action on the sympathetic ganglia, and not to a peripheral autonomic effect. Gunn and Gunn (1914), however, did occasionally observe inhibitory effects on the excised uterus of rats and guinea pigs. *The uterine cervix* in rats is inhibited by epinephrine, unaffected by pitocin (S. Genell, 1940).

Direct Stimulants.—Powerful contractions are produced in nonpregnant as well as pregnant uterus of all animals by *ergot* and its alkaloids, by posterior pituitary extract (Frankl-Hochwart and Froehlich, 1909), by *histamine* (Barger and Dale, 1910); and by related amines, peptones, and *anaphylactoid poisons* (Hanzlik, 1920). *Quinine* and the other cinchona alkaloids may cause strong contractions (Kurdinowski-Kehrer, 1906; Hale, 1915), but are uncertain (Rucker 1921; Frank and Katz, 1922). *Hypotonic solutions* produce contraction (Barbour and Rapoport, 1922).

Demerol increases the contractions of intact human uterus; *syntropan* relaxes (Solomons and Widdess, 1943).

Other drugs which tend to stimulate contractions include *tyramine*; *congo red*; *hydrastine*, *hydrastinine* and *cotarnine*: many *organ extracts* (Fawcett *et al.*, 1915), especially prostate (Macht, 1920), ovary (Itagaki; Athias, 1921) and placenta (Ludwig, 1920). The miscellaneous plants used in proprietary "*female remedies*" have little if any action on the uterus (Delzell *et al.*, 1916; Pilcher, 1917).

The *ratio of potassium and calcium* in the Ringer solution modifies the reactions of the excised uterus (Fate and Clark, 1921; Rosemann, 1923). Excess of potassium weakens and excess of calcium increases the responses to stimulating drugs. Decrease of potassium increases the contractile responses. Absence of calcium prevents stimulation by pituitary, quinine and ergot, but does not prevent stimulation by epinephrine, cocaine or pilocarpine (Inami, 1928).

Reflex Increase of Uterine Movements.—Drastic cathartics and irritant volatile oils produce reflex stimulation of the uterus (Kehrer, 1910). These should therefore be avoided in pregnancy. They are reputed abortifacient, but are highly dangerous. For the excised uterus, moderate concentrations of the *emmenagogue oils* are indifferent, and higher concentrations inhibit (Gunn, 1921).

Antagonists to the Contractor Effects.—Ergotoxine is more effective against epinephrine than against the parasympathetic stimulants; atropine is more effective against these than against epinephrine; however, both depressants are sometimes antagonistic against both stimulants (Cushny, 1910; Dale and Laidlaw, 1912; Gohara, 1920). The relaxing action of epinephrine in the guinea pig and mouse may overcome the barium, histamine and choline stimulation (Sugimoto, 1913; Adler, 1918).

Pregnancy on the Drug Responses of the Uterus.—The change in the response of the pregnant cat uterus to sympathetic stimulation and epinephrine (Cushny, 1921) appears within a few days after conception (Athias) and disappears again within two days after birth (N. B. Dreyer and Moreash, 1933). It must therefore be due to functional sensitization, and not to the development of new muscle fibers, as was suggested by Quagliarielli, 1918. The susceptibility to stimulation by extracts of the *posterior pituitary* also goes through a striking cycle of changes in all animals, decreasing early in pregnancy, then increasing toward term and especially near parturition, and then decreasing promptly thereafter. In normal primiparous women it decreases parallel with the spontaneous contractions, disappearing about the tenth day. It may then be partly restored by administering estrin (W. Bickers, 1942). This pregnancy cycle has been demonstrated on excised human uteri; also in regard to *ergotoxine*, but the response to *histamine* is not altered (M. M. Robson, 1933). It holds for *cocaine* and *quinine*, but it does not appear to apply to *pilocarpine* (Inami, 1928). The dependence of the pregnancy changes on *sex hormones* was established by Van Dyke and Gustavson, 1929, when they showed that treatment with corpus luteum confers the pregnancy responses on the uteri of kittens. It is now recognized that they depend on the changes in the relative preponderance of estrogens, which increase uterine excitability, and progesterone, which allays it.

Vaginal muscle is innervated by the sympathetic. Epinephrine or electric stimulation may cause contraction or relaxation, regardless of the direction of the uterine response; they relax after ergotoxine. Physostigmine and pilocarpine contract, and are antagonized by atropine (review, Gruber, 1933).

Fallopian tubes are usually contracted by epinephrine, but a small dose may inhibit. Atropine relaxes the epinephrine contraction.

Round ligament is relaxed by epinephrine in cats, contracted in rabbits. **Prostate gland** is contracted by both epinephrine and pilocarpine. Epinephrine relaxes after ergotoxine (Waddell, 1916). Extracts of prostate stimulate all genital muscles, and especially the uterus (Macht, 1922).

Seminal vesicles, vas deferens and "uterus masculinus" react like the prostate muscle (Waddell, 1916, and Macht, 1917).

Erectile Tissue of the Penis.—Stimulation of the *parasympathetic* "erigens" branch of the pelvic nerve produces dilatation of the penile arteries and erection. Nikolsky, 1879, claimed that these effects also follow pilocarpine and are antagonized by atropine, but others have reported no effects from parasympathetic stimulants. It is conceivable that they may be negatived by the effects on the general circulation, malaise, etc. Stimulation of the *sympathetic* pudic nerve, or epinephrine, produces constriction of the vessels of the penis and flaccidity (Elliott).

The retractor penis muscle of dog furnishes a striking anomaly. The smooth muscle has a double innervation, the sympathetic being augmentor and the parasympathetic inhibitory (Langley and Anderson). Epinephrine produces contraction and this is antagonized by ergotoxine, as would be expected. The parasympathetic stimulants, however, also produce contraction, that is, they act on the sympathetic and not on the parasympathetic. Similarly, atropine, although it antagonizes the parasympathetic stimulants, does not abolish the response to electric stimulation of the parasympathetic (sacral) nerve. It appears therefore that the action of the parasympathetic poisons has been transposed to the sympathetic division. However, ergotoxine does not antagonize the parasympathetic stimulants. Nicotine stimulates, although there are apparently no ganglion cells (Edmunds, 1920; Zilva, 1901; Bottazzi, 1916; M. J. Oppenheimer, 1938).

The ureter contracts rhythmically when distended with urine; and as its excitability is normally highest at the renal pelvis and lowest at the bladder end, the contractions progress as peristaltic waves which help to propel the urine to the bladder. (The gradient may be reversed, and with it the direction of the peristalsis, by depressing the pelvic end with drugs, etc. C. M. Gruber, 1928.) The ureter peristalsis is increased by stimulation of either the sympathetic (splanchnic and inferior hypogastric) or the parasympathetic (pelvic) nerves, but sympathetic stimulation may also be inhibitory. The sympathetic innervation is more active in the upper portion, the parasympathetic in the lower (Satani, 1919).

Epinephrine increases the rate, tonus and sometimes the amplitude of the ureteral peristalsis. Pilocarpine and other *parasympathetic stimulants* also do so, but generally more feebly. Ergotoxine is more effective against epinephrine, and atropine against parasympathetic stimulants. *Nicotine* first stimulates and then arrests the movements of the excised ureter (Satani). The reactions to the *nonspecialized drugs* are of the usual type: augmentation also results from barium, veratrine (Rossi, 1918), morphine, cocaine, procaine and increased alkalinity. Depression is produced by chloroform (Lucas, 1906), by papaverine and the other isoquinoline alkaloids, by chelidonine, benzyl benzoate, hydrastine and emetine (Macht, 1916, 1916–1918; Roth, 1917). The effects of obstruction on ureteral peristalsis are described by Wislochi and O'Conor, 1921. Sano, 1927, reports that the ureter of gravid rabbits is inhibited by epinephrine and pituitary, stimulated by pilocarpine and barium.

Urinary Bladder and Urethra.—The urinary bladder is an instance of smooth muscle subject to central control, and voluntary in normal micturition. This is affected by contraction of the smooth muscle of the *body of the bladder*, whose motor innervation is chiefly parasympathetic by the pelvic erigentes nerves, with ganglion cells in the bladder wall. Its sympathetic innervation, through the hypogastric nerve with relay cells in the inferior mesenteric ganglion, is less potent and chiefly relaxant. The *trigone of the bladder* (including Bell's muscle; Gruber, 1935) and the muscular fibers of the *urethra*, which function as the *sphincter* to the bladder, have different and reciprocating autonomic reactions. They are strongly contracted by epinephrine stimulation, and rather feebly relaxed by parasympathetic stimulation (Elliott). *Evacuation of the bladder* is effected chiefly by the parasympathetic stimulation of the body of the bladder, probably with some inhibition of the sympathetic tonus of the trigone and urethra. The *autonomic drugs* act in close accordance with the innervation, both in excised bladder and in living animals.

Pilocarpine contracts the body of the bladder, and increases the intravesicular pressure (Graf and Froberg, dogs, 1933). The trigonal region is generally not affected, but may be contracted. Choline and its esters (Winters, 1940) and physostigmine and prostigmine act similarly, and the latter is used clinically against postanesthetic paresis of the bladder. (The cholinergic mechanism shows certain peculiarities; V. E. Henderson and Roepke, 1935.) *Atropine* relaxes the parasympathetic contraction. Considerably larger doses are required against electric stimulation of the nerve than against pilocarpine. It tends to lower the normal intravesicular pressure in children and is often useful against enuresis (Amberg and Gros, 1931). It is not effective against the violent contractions of urethral obstruction, nor is hyoscyamine. These can only be allayed by deep ether or chloroform anesthesia. I. C. Winters, 1940, reports increased bladder tonus and decreased capacity, similar to morphine, in unanesthetized dogs. *Epinephrine* gives somewhat different reactions according to the kind of animal (Elliott, 1905), dose and other conditions. In general, moderate doses tend to relax the body of the bladder, especially if the tonus was high (Griffiths). It therefore antagonizes parasympathetic stimulation and ergotoxine. With other doses, the epinephrine relaxation may be followed by contraction. The trigone region is generally contracted (Edmunds and Roth). It also provokes contraction of the posterior urethra (Elliott; Flagge; Young) and thus increases the resistance to bladder outflow. The intravesical pressure is briefly increased (Graf and Froberg). *Ephedrine* does not act on the bladder like epinephrine (MacDonald and M'Crea, 1930). In unanesthetized dogs, it relaxes the tonus and increases the capacity (Winters, 1940). *Ergotoxine and ergotamine* reverse contractor responses to epinephrine, but not the inhibitory effect (MacDonald and M'Crea, 1930). Excess of calcium also diminishes contractor and favors relaxor response of excised bladder (Streuli; Chiari and Frohlich).

Urethral resistance to micturition, in unanesthetized dogs, is diminished by acetylcholine, mecholyl, scopolamine, atropine and morphine; increased by pilocarpine, physostigmine, neosynephrine, amphetamine, and ephedrine; epinephrine has no effect. *The irritability of the bladder* is increased by scopolamine, atropine, morphine, physostigmine, and neosynephrine; lowered by amphetamine and ephedrine (I. C. Winter, 1941).

Miscellaneous Drugs.—These generally act alike on all regions of the bladder. *Ether anesthesia* produces relaxation. *Morphine* and *ephedrine* may cause spastic retention, the former, at least, probably by central stimulation of the urethral muscles. *Pituitrin* and barium contract (histamine does not; Abelin, 1919). The barium and pituitary constriction can be overcome by epinephrine, and barium by atropine; at least in frogs (Adler, 1918), whose bladder shows less differentiation and contracts both to sympathetic and parasympathetic stimulants (Langley). The *literature* to 1933 is reviewed by Gruber.

AUTONOMIC REACTIONS OF THE EYE

The iris is controlled by two reciprocating sets of muscle fibers, the circular sphincter with oculomotor innervation of parasympathetic type; and the radial dilators, innervated from the superior cervical ganglion. The dilator-sympathetic set is concerned mainly in the pupillary changes of emotion (Ingalls, 1923) and in asphyxia. The changes of the pupil for vision are effected mainly by the oculomotor-sphincter set, which also controls the ciliary muscle. The sphincter receives continuous tonic constrictor impulses from the pupillary center, the tone of which is being continuously inhibited, but to a varying degree, by afferent and emotional impulses. The diameter of the pupil is the resultant of these opposing forces. Peripheral autonomic reactions are produced through stimulation and paralysis of (*a*) the ganglia of both systems by nicotine; (*b*) stimulation of the sympathetic receptive mechanism by epinephrine and cocaine (mydriasis); and (*c*) paralysis of the oculomotor receptive mechanism by atropine (mydriasis); and its stimulation by pilocarpine, choline, physostigmine and the related drugs (miosis).

The localization of the oculomotor reactions offers interesting problems: *Atropine* dilates the pupil. Stimulation of the short ciliary nerve, *i. e.*, of the postganglionic fibers of the oculomotor, fails to constrict the pupil. Atropine must therefore have paralyzed the sphincter mechanism peripherally to the ganglia. Direct electric stimulation of the sphincter muscle still produces contraction; so that the contractility of the muscle is not injured. The atropine must therefore act on the nerve endings, or on the receptive mechanism. As we are dealing with a paralysis, degeneration of the nerve could not be employed to distinguish between these. Recourse must be had to the indirect method of matching atropine against pilocarpine.

If the short ciliary nerve is divided and allowed to degenerate until it becomes irresponsive to electric stimulation, *pilocarpine* still produces miosis (Anderson). It must therefore stimulate peripherally to the degenerable oculomotor endings. Atropine, however, removes the miosis; from this it follows that the pilocarpine does not directly act on the contractility of the muscle, for this is not affected by atropine, as was shown above. The pilocarpine must therefore stimulate the receptive mechanism. The experiment also shows that the atropine action can not reside in the nerve endings, for in that case it could not antagonize the effects of pilocarpine peripheral to these endings. This therefore also localizes the atropine action in the receptive mechanism. Although *physostigmine* is more potent than pilocarpine against atropine mydriasis, it is not miotic after nerve degeneration, because it does not act directly, but prevents the decomposition of acetylcholine, which is apparently present only when the nervous mechanism is intact.

The response of the iris to physostigmine disappears within a few days after section of the nerve; that of the fibrillary contractions of striped muscle only between the eighteenth and twenty-seventh days (Magnus, 1908). The response of the iris returns after about ten weeks, probably by regeneration of the postganglionic fibers (I. H. Leopold and Comroe, 1945).

The *iris of guinea pigs* reacts typically to atropine, muscarine, physostigmine and arecoline, but *pilocarpine* is mydriatic and antagonistic to the parasympathetic stimulants. If the iris is denervated, it becomes constrictor (Koppanyi, 1929). *Rats* react similarly (Koppanyi and Sun, 1926). R. D. Barnard, 1943, attributes the paradoxic mydriasis of rat eyes to cholinergic drugs, especially cyanamide, to pressure of the engorged harderian glands on the optic nerve, cutting off the reflex pupillodilator tonus.

Conflict of Sympathetic and Parasympathetic Actions.—Langley and Dickinson, 1890, showed that the effects of *nicotine* on the pupil and nictitating membrane are the result of simultaneous stimulation of the sympathetic and cranial innervation. In cats, the sympathetic usually predominates (dilatation of pupil and retraction of membrane). Pilocarpine, on the other hand, causes constriction (oculomotor stimulation), which is also unaffected by complete denervation (Anderson). It acts also on the sympathetic, however, for the nictitating membrane retracts. Both drugs therefore act on both systems.

Both drugs act after degeneration of the nerves, in the body; but with the excised iris, only the augmentor (oculomotor) response persists. To explain this contradiction, Dale and Laidlaw, 1912, assume that the sympathetic stimulation in denervated animals is brought about by increased secretion of epinephrine, to which the denervated sympathetic endings are especially susceptible.

Excised Iris.—In dogs, beef and cats the central region consists exclusively of circular (sphincter) fibers, the outer predominantly of radial (dilator fibers). The two regions react qualitatively alike to the autonomic drugs; *i. e.*, both are constricted by the cholinergic and dilated by the adrenergic stimulants (Leyko, 1927). The dilator effect of the sympathetic stimulants on the inner region must be by inhibition of the tonus of the circular fibers; in the outer region the radial fibers are also stimulated.

The reactions of the radial-free *iris sphincter* are as follows: *Epinephrine* dilates, even in dilution of 1:400,000,000, effective also after physostigmine; epinine, cobefrin and arterenol act like epinephrine. *Ephedrine*, amphetamine and neosynephrine dilate occasionally; *cocaine* may dilate, also after atropine. *Pilocarpine*, *choline* and its esters and *physostigmine* constrict; physostigmine sensitizes to acetylcholine and mecholyl, not to pilocarpine. They are antagonized by *atropine*, and feebly by the sympathetic stimulants. *Barium* and *ergotoxine* constrict, and are but slightly antagonized by atropine. *Histamine* constricts in dilutions of 1:1,000,000,000 (Yonkman, 1931; Gunter and Mulinos, 1939).

Excised Iris of Frog and Eels.—These show rather peculiar reactions: in the excised bulbus, atropine (2 per cent) or cocaine (2.5 per cent) dilate; but no contraction is produced by pilocarpine, physostigmine, nicotine or muscarine, 0.1 to 2 per cent (Magnus, 1899).

Iris of Striated Muscle.—The iris of birds consists of striated muscle, and responds to drugs like other striped muscle; *f. i.*, it is paralyzed by curare. The iris of the *alligator* also consists of striated muscle, but is innervated like the constrictor iris of mammals, and responds to the autonomic drugs, as does also the iris of the *turtle* (Iske, 1929).

Clinical Susceptibility of Iris.—K. K. Chen and Path, 1929, found that the susceptibility to the sympathetic mydriatics (cocaine, enophthalmine and ephedrine) is greater in Caucasians than in Chinese, and least in Negroes. Gnad, 1930, reported that blue iris is much more responsive than brown to all kinds of pupillomotor drugs.

The ciliary muscle has exclusively parasympathetic innervation. Physostigmine and pilocarpine produce spastic contraction, and fix accommodation for near vision. Atropine relaxes the static tonus, more than any other agent, and fixes accommodation for distant vision. Sympathetic stimulants (epinephrine and cocaine) do not affect the static tonus, but they reduce the range of accommodation (Hartgraves and Kronfeld, 1931). The range of accommodation is greatest at birth and decreases steadily as *age* progresses (J. S. Friedenwald).

Intra-ocular pressure is markedly affected by the parasympathetic drugs, especially in glaucoma when the margin of safety for the drainage of the intra-ocular fluids is small. The drainage canals in the ciliary margin are mechanically compressed by the attachments of the ligament of the lens when the ciliary muscle is relaxed by atropine, and are opened by physostigmine or pilocarpine. Sympathetic mydriatics have little effect on the drainage, but epinephrine may raise the intra-ocular pressure by the rise of blood pressure. Nitrites may raise it by dilating the ocular vessels.

The *filtration of organic dyes* from the blood into the aqueous humor of rabbits was reported increased by physostigmine and pilocarpine, and decreased by atropine and epinephrine (Sawada and Mizuta, 1927). Wesselkin, 1929, found it increased by all agencies that cause congestion or increase intra-ocular pressure, including intravenous injection of epinephrine. The penetration of intravenously injected arsphenamine and tryparsamide into the aqueous humor is also increased by conjunctival application of pilocarpine or physostigmine (A. C. Krause *et al.*, 1930).

The extrinsic muscles of the eye are the only mammalian striated muscles which respond like the muscles of the lower vertebrates and like denervated or innervated fetal muscle to choline and nicotine, *i. e.*, by tonic contracture (Duke-Elder, 1930). **The nictitating membrane** of cats is contracted by parasympathetic stimulants, augmented by cocaine, inhibited by atropine (Rosenblueth, 1932). *After ergotoxine*, it responds to epinephrine and noradrenaline by relaxation; to nerve stimulation or acetylcholine by contraction, followed by relaxation (Acheson, 1940).

AUTONOMIC REACTIONS OF BRONCHIAL MUSCLE

The smooth muscle of the air passages in mammals, extending from the trachea to the beginning of the infundibula, is innervated solely by the vagi, which carry mainly constrictor, but also dilator fibers—the latter sympathetic—from the stellate ganglia. It responds both to parasympathetic and to sympathetic drugs. The parasympathetic stimulants produce constriction; atropine, relaxation. Epinephrine results in relaxation, especially if the muscle was contracted; ergotoxine causes constriction. The bronchial muscles contract violently to the nonspecialized muscular stimulants, barium, etc.; and especially to histamine, peptone and other anaphylactoid poisons, and to true anaphylaxis. Hypersusceptibilities of this type constitute one group of bronchial asthmas. Bronchial spasm may also be produced reflexly, as by irritant vapors. Direct muscular depressants, such as nitrites, relax the bronchioles. Constricting and dilating agents are mutually antagonistic, regardless of their mechanism of action.

Methods.—Bronchial reactions were studied in intact animals by Dixon and Brodie, 1903, and by Sanoz, 1914, by recording the excursions of the lungs under uniform artificial respiration. These, however, can be altered also by cardiac dilatation, pulmonary congestion or edema, and by changes of the blood volume and blood pressure. D. E. Jackson, 1913, introduced a compensator to keep the blood pressure constant, but the other possibilities are not easily eliminated in intact animals. The results should therefore be checked on excised bronchi. Rings of bronchial muscle suspended in a saline bath were used by Trendelenburg, 1912; Macht and Ting, 1921; and others. They are restricted to relatively large bronchi. Sollmann and von Oettingen utilized the resistance of the bronchial tree of excised lung to the flow of saline solution infused through a tracheal cannula. The most direct method is the microscopic observation of the bronchioles of all sizes in free hand sections of lungs, suspended in warm oxygenated saline, as described by Sollmann and Gilbert, 1937. The results of the various methods are in general agreement: for instance, Jackson, 1914; Wornant, 1929; Swanson, 1929; Swanson and Webster, 1930 (including perfusion); Miyake, 1929 (excised); Sollmann and Gilbert, 1937 (microscopic). There are some peculiar differences in the reactions of various kinds of animals: for instance, the bronchioles of rats do not react to histamine; those of rabbits but feebly to epinephrine. Human bronchial muscle is highly susceptible (Sollmann and Gilbert).

Bronchial Movements.—Direct microscopic observations show that normal bronchioles may execute spontaneous rhythmic pendular and peristaltic contractions, or undergo more lasting changes of tonus. They react in the traditional manner to drugs and anaphylaxis, constricting to actual occlusion. The alveoli and infundibula do not react to any of the drugs. The spontaneous rhythmic movements have not been recorded in the intact lung (T. Gordonoff and Scheinfinkel, 1936), because of mechanical difficulties. There can be little doubt that they occur normally, for the vigor and tension are more favorable to them *in situ* than in sections. Their *function* is problematical, but they would tend to offset the dead space of the lungs by alternately shifting the resistance and thus securing more effective air currents. They also tend to diminish firm adherence of the mucus; but they could not effectively propel and expel the mucus, except for short distances. The tonus of the entire bronchial tree could vary the total dead space of the pulmonary air way. It is tempting to assume that it may adapt this to the rate and depth of breathing. It runs riot in the spasm of allergic asthma. The dilatation of the bronchi in inspiration and contraction in expiration, as observed with the bronchoscope (M. Ellis, 1930), are purely passive adjustments to the intrathoracic pressure (H. C. Nicholson and Trimby, 1940).

Bronchial constriction is produced by parasympathetic stimulants (mecholyl, pilocarpine, physostigmine); by histamine (not effective in rats) and less powerfully by anaphylaxis, barium, nicotine, cyanide, benzedrine. Chloroform and ether produce slight constriction, sometimes followed by dilatation (microscopic observation, Sollmann and Gilbert). Other methods have shown that the following also produce bronchial constriction: Choline, arecoline, muscarine; morphine, thebaine, dionin; ergotamine (slight), potassium, calcium (D. E. Jackson, 1914; Swanson, 1929). In intact animals, nicotine, lobelia and curare and small doses of pilocarpine produce an initial constriction, followed by dilatation. Jackson attributes this secondary dilatation to stimulation of the suprarenals. This dilatation is also produced by acetylcholine if it is preceded by atropine and ergotamine, but does not occur if the adrenal glands have been removed (Melville, 1938).

Bronchial constriction from higher centers, directly or reflexly, is produced by cerebral anemia, nasal insufflation of ammonia, nicotine, cyanide and barium (Houssay and Cruciani, 1929).

The anaphylactic response may be observed microscopically on sections of the lungs of rabbits sensitized by injection of egg albumen. Such bronchioles are constricted by the addition of egg albumen, which has no effect on unsensitized bronchioles. The spasm passes off spontaneously in a few minutes, and can not be repeated by further addition of albumen. The sensitized or desensitized bronchioles respond to drugs in the normal manner (Sollmann and Gilbert).

Anaphylaxis in intact animals includes congestion and edema of the bronchial mucosa. In clinical asthma this is further complicated by chronic inflammatory changes.

Bronchial dilatation may be observed microscopically with atropine and epinephrine (epinephrine acts feebly in rabbits). These dilate normal bronchioles, and both antagonize equally parasympathetic and muscular constrictors. Papaverine, dilute acid, ephedrine, magnesium and nitrite dilate more weakly. Other methods confirm these dilatations and show that hordenine, lobeline, caffeine and metrazol also dilate. Cocaine intensifies the dilator action of epinephrine and antagonizes ephedrine and especially pseudoephedrine. Sympathetic denervation by excision of the stellate ganglia also intensifies epinephrine dilatation (Co Tui *et al.*, 1936). Iodides have no effect in living animals. They dilate excised bronchial muscle (Macht and Ting, 1921), but only with concentrations much higher than could be maintained in the blood.

Antagonisms.—Bronchial constriction by parasympathetic stimulants, histamine or anaphylaxis, and dilatation by atropine, epinephrine or papaverine neutralize each other without reference to the mechanism or site of their action, according to the observations of Sollmann and Gilbert. This agrees generally with the lung plethysmograph method, except that Swanson, 1929, reports atropine ineffective against histamine and morphine constriction. Epinephrine may dilate after ergotamine, but not after F 933 (Melville, 1938).

Pseudospasm of Bronchi.—*Agar solutions* perfused through the pulmonary artery of guinea pigs produce marked distention of the lung and arrest of perfusion flow. The effect is not antagonized by papaverine or atropine, and is due to agar emboli in the pulmonary vessels. These arrest the circulation and shut off the bronchi by mechanical compression (Hanzlik and Karsner, 1920).

Lower Vertebrates.—In snakes and turtles, the innervation and the response to drugs are as in mammals: contractor to parasympathetics; relaxor to epinephrine, except that the relaxor effect of epinephrine is weak (Carlson and Luckhardt, 1920; Luckhardt and Carlson, 1921). Nicotine, pituitary, lobeline and veratrine produce strong contraction of the turtle lungs, which is not observed in dogs. Codeine and pilocarpine act as in mammals (D. E. Jackson and Pelz, 1918).

In *frogs* and *salamanders,* the musculature of the lung sacs corresponds to the bronchial muscle of mammals, but has a different physiology and innervation (frog, Carlson and Luckhardt, 1920; salamanders, Luckhardt and Carlson, 1910). The muscle possesses a strong and continuous inherent tonus, which is relaxed by parasympathetic (vagus) stimulation, and is highly augmented by sympathetic stimulation. The response to epinephrine is transposed; *i. e.,* it produces relaxation. Atropine presents another anomaly, for it does not prevent the inhibiting response to vagus stimulation. Pilocarpine, which was tried only on salamanders, acts normally, *i. e.,* relaxes. Contraction of frog lung by acetylcholine is a more sensitive assay method even than leech muscle (M. Corstein, 1940).

D. Potick, 1943, also reports that the smooth muscle of frog and toad lung is contracted by cholinergic and relaxed by adrenergic drugs. Histamine has little effect; pituitrin has none.

The **ciliated epithelium of the respiratory** passages extends from the turbinates through the trachea nearly to the terminal bronchioles. In mammals it is not supplied with nerves (Plattner and Hou), and is not affected by most of the autonomic drugs, except as they may affect the mucous covering and thereby the mechanical resistance to the beating of the cilia. A thin film of fluid mucus is moved outward fairly rapidly (twelve to twenty-three seconds per millimeter in the trachea of living guinea pigs) as on a rolling sidewalk (Henschen), and with it any dust and carbon on their surface; but the force is weak. Thick, viscous mucus is moved slowly. The cilia are markedly affected by temperature; 36° to 38° C. is optimal for mammalian bronchi (Gordonoff, 1938); human nasal cilia are most active between 65° and 85° F. These are arrested between 45° and 55° F., but are restored by warming (Proetz, 1934). They are depressed by impairment of circulation (Lommel, 1908).

With *human mucosa* extirpated from the nose, chlorbutanol inhibits ciliary motion; sulfonamides and penicillin have no effect (Lierle and Evers, 1944). On the intact *mucosa* of the turbinates of guinea pigs, *epinephrine* 1:1000 depresses (probably by its chloretone). *Ephedrine* hydrochloride, 3 per cent, and *cocaine* hydrochloride, 5 per cent, are not detrimental; 10 to 20 per cent cocaine slows, but with good recovery. *Menthol, thymol* and *eucalyptol*, 0.5 to 1 per cent, are mildly depressing. *Mild silver protein*, 5 to 20 per cent, has little effect. *Mercurochrome*, 2 per cent, and *zinc sulfate*, 2 per cent, depress. *Silver nitrate*, 0.5 per cent, kills the cilia immediately, without recovery (Lierle and Moore, 1934).

Tracheal and bronchiolar cilia are depressed in *living animals* by large doses of *alcohol* (Herrmann, 1933) and by general anesthetics, chloroform, ether, ethyl chloride, avertin and evipal (A. M. Ernst, 1938), perhaps by depression of the circulation. In *excised bronchioles* (thin sections) most autonomic drugs have no visible effect. *Nicotine* arrests, but this requires rather high concentration (1:2500). *Chloroform, ether* and *cyanide* also arrest (Sollmann and Gilbert, 1937). The *tracheal cilia of the turtle* behave similarly to the mammalian (Lucas and Douglas, 1935).

The reactions of the cilia of frog's pharynx differ materially from those of mammals and turtles. They have a *parasympathetic* innervation (Lucas, 1935), and their beat is accelerated by parasympathetic stimulants (pilocarpine, choline and its esters, arecoline). *Atropine* antagonizes these, but has no effect alone. *Epinephrine* has no effect; nor has morphine, potassium chloride, or 5 per cent alcohol. *Camphor* accelerates. *Nicotine, chloral, ether, quinine, caffeine* and *calcium* depress (S. Ishikawa and Ohzono, 1931; Plattner and Hou, 1931).

The ciliary action of paramecium is reversed by monovalent cations (Mast). The order of potency decreases in the direction $K > Li > Na > NH_4$. It is independent of the anion (Oliphant, 1938). It responds to drugs that act directly on smooth muscle, but not to those that act on the nervous mechanism (J. F. Oliphant, 1943.)

AUTONOMIC REACTIONS OF THE HEART

The parasympathetic innervation of the heart is inhibitory. It comes by the vagus, and its ganglia are intracardiac. The sympathetic is augmentory, with its ganglia in the annulus of Vieussens. *Nicotine* at first stimulates and then paralyzes the ganglia of both divisions; the vagus effect predominates ordinarily. Nicotine therefore renders the heart irresponsive to stimulation of the vagus trunk; but stimulation of the postganglionic fibers, in the sinus region, still arrests the heart.

Parasympathetic Drugs. — Atropine destroys the response to postganglionic as well as to preganglionic vagus stimulation. The muscle is not paralyzed, since the heart continues to beat with undiminished vigor; the action of atropine must therefore be between the ganglia and the contractile mechanism, in the receptive mechanism. *Parasympathetic stimulants*, acetylcholine, muscarine, physostigmine and pilocarpine, weaken and slow the heart and produce diastolic arrest, and are mutually antagonistic with atropine. The pilocarpine effect, however, is liable to change to vagus paralysis.

Orthosympathetic Drugs.—Epinephrine increases the rate and amplitude of the contractions; this is prevented by *ergotoxine*, but only slightly modified by F 933 (W. T. Hill and Myers, 1939).

Ion Ratio.—Increase of the $\frac{Ca}{K}$ ratio stimulates sympathetic stimulation, and renders the sympathetic more sensitive and the parasympathetic less sensitive to stimuli (Burridge, 1912). Conversely, increase of the $\frac{K}{Ca}$ ratio favors parasympathetic stimulation. Radio-activity acts like potassium (Zwaardemaker, 1918).

Nonspecific Drugs.—Barium, the digitaloid drugs and caffeine stimulate the force of the heart, and quinidine depresses. Their relation to the autonomic system is obscure, but they appear to act more directly on the contractile substance.

Composite Effects.—When the heart is subjected simultaneously to poisons belonging to different groups, they may add their actions in a simple manner; for instance, the acetylcholine inhibition may be removed either by paralyzing the inhibitory mechanism with atropine, or by stimulating the augmentory mechanism with epinephrine (Barlow and Sollmann, 1926). However, discordant effects from such combinations have been reported, especially by Kolm and Pick, 1920, and Amsler, 1920, which these investigators interpret as transfer of the action from one system to the other. They conceive that these drugs are really "amphotropic," *i. e.*, that epinephrine may stimulate the parasympathetic as well as the sympathetic; but that the normal sympathetic effect so greatly overshadows the parasympathetic that the latter is only observed when the parasympathetic system is especially sensitive, or when the sympathetic system is especially insensitive.

Central Effects.—The heart rate is normally regulated by tonic and reflex stimulation from the higher parasympathetic and sympathetic centers, especially in the hypothalamus. The *clinical reactions* to therapeutic doses of epinephrine, atropine, ergotamine, pilocarpine and physostigmine may therefore differ from what would be expected from their peripheral actions (H. Freeman and Carmichael, 1936).

The effects of *direct application to the hypothalamic centers* are described by Dikshit, 1934.

After complete removal of the sympathetic chain, the cardiac rhythm of dogs is slower, and emotional excitement produces less acceleration than in normal animals. Cardiac acceleration in dogs, therefore, normally involves stimulation of the sympathetic as well as decreased tonus of the cardiac inhibitory centers (Brouha *et al.*, 1936).

The *distribution of the parasympathetic innervation* varies in different animals. In mammals, the chronotropic fibers of the vagus go chiefly to the sino-auricular node, and thereby set the rate of the whole heart. In isolated rabbit's or cat's heart, acetylcholine, arecoline and pilocarpine act most potently on the Keith-Flack node, then the Aschoff-Tawara node, and much less on the lower ventricular node. With epinephrine, the difference is much less, but in the same direction (Anitschkov, 1934). *Auriculoventricular conductivity* is depressed by vagus and enhanced by sympathetic stimulation. Choline esters depress the conductivity and are potentiated by physostigmine, prevented by atropine; epinephrine enhances the conductivity and is mutually antagonistic with parasympathetic stimulants. Asphyxia first increases then depresses the conductivity (Carlen and Katz, 1939). The inotropic vagus action is distinct from the chronotropic action in dogs, and is believed to be exerted directly on the muscle fibers of the atrium. None of the vagus fibers go to the ventricle in dogs. Stimulation of the left vagus depresses the conductivity and increases the refractory period of the auriculoventricular node, so that the ventricles are slowed more than the auricles, and strong stimulation produces complete heart block. In turtles also, physostigmine slows or stops the rhythm of sino-auricular and auricular, but not of the ventricular segments (Greene, 1932). Pilocarpine and acetylcholine do not inhibit ventricular segments, indicating that the turtle ventricle does not have a parasympathetic receptive mechanism. Its sympathetic innervation is also weak, responding but slightly to epinephrine (Hiatt and Garrey, 1943).

Seasonal Variations in Vagus Response.—During the summer, frogs show a markedly diminished response to vagus stimulation, electrical or by drugs (Cori, 1921; Langecker, 1924). Cori showed that this is not due to altered K and Ca content, and attributes it to thyroid changes

Effect of Epinephrine on Vagus and Accelerator Response.—Vagus stimulation is unable to slow the heart against the maximal stimulation of epinephrine (Kuroda and Kuno, 1916), but smaller doses lower the threshold of vagus stimulation for frogs. Stimulation of the accelerator nerve does not add materially to the augmentation produced by epinephrine, so that the response to accelerator stimulation appears diminished or abolished (Barlow and Sollmann, 1926).

Sensitization by Other Conditions.—In thyroid intoxication the intact heart responds much more than normally to both mecholyl and epinephrine (B. Wise and Hoff, 1938). The presence of *nonelectrolytes* (urea, sugar) renders the heart more resistant to calcium deficiency; which Loewi (1921) interprets as sensitization to the smaller quantities of calcium that remain. The nonelectrolytes also sensitize to strophanthin; they may therefore be classed with the sensitizers of sympathetic action. Treatment of the heart with *lecithin* and *soap* renders it more resistant to choline and pilocarpine, *i. e.*, diminishes parasympathetic stimulation (and by heat). Ergotomine blocks the vagus augmentation. Curare, erythrine, *serum* antagonize parasympathetic stimulation (muscarine), and increase the parasympathetic depression of atropine. This is due partly to its calcium, partly to the ether-soluble extractives (Kirste, 1921). Increase of *alkalinity,* within physiological limits (to pH 7.8) increases the tonus (Andrus, 1919); *i. e.*, acts in the sympathetic direction. The response to vagus stimulation in frogs is diminished by increase of intra-auricular pressure, and by caffeine (Barry, 1929).

Crustaceans react distinctively. The *crawfish* heart is quickened by acetylcholine; atropine is antagonistic. *Crab* (cancer) heart responds to this by increase of tonus without change of rate. Pilocarpine stimulates, atropine antagonizes, epinephrine also stimulates, ephedrine does not (Bain, 1929). *Daphnia* resembles the vertebrate heart reactions rather than that of the higher crustaceans. Acetylcholine depresses the rate and force; atropine and physostigmine produce irreversible toxic inhibitions; epinephrine accelerates, potassium slows (E. R. Baylor, 1942). Acetylcholine accelerates the heart of the higher *arthropods,* some annelids and some tunicates, and slows the rate in most molluscs (C. L. Prosser, 1942; Davenport *et al.*, 1940).

The lymph hearts of frogs and toads contain striped muscle and therefore react differently. These are arrested by sympathetic and quickened by parasympathetic nerve stimulation (and by heat). Ergotamine blocks the vagus augmentation. Curare, erythrine, acetylcholine, nicotine and digitalis arrest; physostigmine, veratrine and ouabain decrease the amplitude; pilocarpine, atropine and pituitrin have no effect (Hotovy, 1939; Braun-Menendez and Foglia, 1940). If all four lymph hearts of the toad are destroyed, death occurs in two to four days, with progressive increase of body weight and concentration of the blood, due to accumulation of water in the lymph sacs. One of the lymph hearts, beating efficiently, suffices for survival (Foglia, 1939).

AUTONOMIC REACTIONS OF THE BLOOD VESSELS

Most blood vessels are innervated only by the orthosympathetic. This has generally augmentory functions which are under continuous tonic control by the vasomotor center. The caliber of the vessels is adjusted chiefly by increase or decrease of these central tonic impulses. In a few situations there is a special vasodilator innervation, generally if not always parasympathetic; for instance, the chorda tympani and the nervus erigens. However, the vessels with purely orthosympathetic innervation respond more or less to the parasympathetic drugs, the stimulants generally being dilator. It may be assumed that they possess the parasympathetic receptive mechanism, but that this has not made connection with the central nervous system.

Dilute epinephrine also often produces dilatation. The arteries and veins show similar phenomena. The capillaries exhibit some special features.

Unusual Innervations.—Reversal of the ordinary innervation is seen in *lung vessels of frogs and turtles.* This is entirely parasympathetic, constrictor in the frog, constrictor and dilator in the turtle. It reacts, however, to epinephrine, which is antidoted by atropine (Luckhardt and Carlson, 1921). The *placental vessels* do not receive any nerves, but react in the usual direction to epinephrine (in the human), barium, histamine and adenosine (von Euler, 1938). The *yolk sac vessels* of chick embryos give opportunity for studying the reactions of vessels before they connect with nerves (Nakatano, 1935).

Dilator Action of Epinephrine.—Under certain conditions, the sympathomimetic constrictor action of epinephrine gives place to nonsympathetic dilator reactions. This is the predominant effect in some vessels (Rothlin, 1921); in others it is seen only with dilute solutions. It may also be evoked by lowering the sensitivity of the sympathetic innervation.

Parasympathetic Drugs. — *Acetylcholine* produces marked vasodilatation, which is antagonized by *atropine* (Hunt, 1918). The effects of *pilocarpine* are also dilator in most cases; but a few contractor reactions have been described (Langley, 1921). Brodie and Dixon found that atropine removes the pilocarpine constriction without impairing the response of electric stimulation of the vasoconstrictor nerves. Hildebrandt (1920) reports that *atropine* antidotes epinephrine and sympathetic nerve stimulation in frog's vessels. It is not antagonistic to barium, but removes veratrine constriction (Kondo, 1919).

Responses of Different Vascular Areas.—The orthosympathetic nerves to dogs' muscles contain cholinergic *vasodilator fibers*; those to the skin do not; those to the intestines contain some. The muscles of rabbits and monkeys are not supplied with sympathetic vasodilators; cats have a small supply; dogs and hares have many (J. H. Burn, 1938). The *human hand* has highly selective arterial reflexes distinct from those of the skin (A. B. Hertzman, 1941). Data for various drugs have been collected on animals by Amsler and Pick (1919) (frog perfusion experiments, splanchnic areas and legs), Adler (1912) (ditto, lung and skin vessels), and Rothlin (1921) (rings of mammalian artery). The vessels of the toes are much less susceptible to vasodilating drugs (papaverine, mecholyl, histamine) than are those of the fingers (E. V. Allen and Crisler, 1937).

The *reactions of systemic arteries* are illustrated by the *excised carotid artery:* In rabbits (also in dogs and cats), *epinephrine* produces marked constriction. This is completely antagonized by *nitrite. Histamine* and *barium* cause marked constriction; *mecholyl;* dilatation. *Anaphylaxis* (egg albumen in sensitized rabbits) had no effect (Sollmann and Gilbert, 1938).

Veins react similarly to arteries, but more feebly (review, K. J. Franklin, 1928). Excised *human veins* were *contracted* by epinephrine, physostigmine, histamine, strophanthin, barium, nicotine and often by caffeine. They are dilated by nitrite (Maloff, 1931). With perfused colic and superior mesenteric vein of cats, Fleisch, 1931, found epinephrine always constrictor with the threshold of 1:10^8. Acetylcholine dilated in 1:10^{11}, higher concentrations constricted; histamine dilated in 1:10^{12} to 10^9 and constricted in 1:10^6.

Vasomotor ganglia are first stimulated, then paralyzed by nicotine. They are also paralyzed by curare and large doses of strychnine and brucine (Langley, 1918).

Ion Ratios.—Calcium excess acts as parasympathetic stimulant to the vessels and as sympathetic stimulant in the heart. The vessels are dilated, and the constrictor response to sympathetic nerve stimulation and to epinephrine is diminished; they may even respond by dilatation. *Calcium deficiency* acts as a sympathetic stimulant on the vessels and as a parasympathetic stimulant on the heart. The vessels are constricted and the constrictor response to epinephrine is enhanced. *Potassium excess* acts as sympathetic stimulant to the vessels; as a parasympathetic stimulant on the heart. The vessels are constricted. However, the effect on epinephrine is abnormal; the constrictor effect is diminished or may even be replaced by dilatation. *Potassium deficiency* also acts as a sympathetic stimulant to the vessels, as well as to the heart. The vessels are constricted and react more effectively to the constrictor action of epinephrine. *Akalinity increase:* Moderate increase acts in the direction of sympathetic stimulation for the vessels, as for the heart; *i. e.*, perfused vessels constrict. This is not antagonized by ergotoxine (Heymann, 1921). Moderate alkalinity also promotes the contractions and tone of excised arteries (Opitz, 1920). Large excess of alkalinity relaxes (Heymann). *Diminished alkalinity* constricts the perfused vessels (Pearce, 1913). The mechanism is not clear; the constriction is prevented by ergotoxine, so that it might be considered as sympathetic; but the constrictor response to epinephrine and to nerve stimulation is abolished or replaced by a dilator response (Heymann; Schmidt). Larger *excess of acid* dilates the vessels; the dilator concentration coinciding with the H ion concentration that stimulates the respiratory center (Adler, 1921). Increase of either acidity or alkalinity favors the production of edema in the perfused frog leg or rabbit ear (Heymann, 1921). *Spleen extract* sensitizes to the pressor (sympathetic) responses of epinephrine; and antagonizes the depressor response (Collip, 1920).

The pulmonary arterioles have given conflicting results. They respond feebly if at all to epinephrine and amphetamine. They are constricted by parasympathetic stimulants (mecholyl, acetylcholine; but pilocarpine dilates) and muscular stimulants (barium, histamine and temporarily by anaphylaxis). Atropine hinders all these agents (A. J. Gilbert, 1938, microscopic section). Foggie, 1937, claims that small doses of epinephrine dilate and large doses constrict. Daly and von Euler, 1932, found epinephrine generally constricting in dogs; acetylcholine sometimes dilated (review of pulmonary and bronchial circulation, Daly, 1933).

Coronary Vessels.—The parasympathetic innervation appears to be generally constrictor; the sympathetic, dilator (Anrep and Segall, 1926); but their susceptibility varies in different animals. Generally, they are *constricted* by choline and its esters, but more powerfully by pitressin. Barium and digitalis are also constrictors. *Dilating* are epinephrine (but varying with species); atropine (against parasympathetic stimulation); nitrite; carbon dioxide, lactic acid, anoxia and cyanide by local action; caffeine and other methylxanthines, adenine and adenylic acid. Histamine dilates in man, dog and cat; it constricts in rabbit. Potassium and strophanthin give indecisive results (Orzechowski, 1933; F. M. Smith *et al.*, 1926). In *dogs*, the vagi carry only cholinergic dilator fibers, which are tonically active. The stellate ganglion sends adrenergic dilator and constrictor fibers, both tonically active, but with constrictor tonus dominant (L. N. Katz and Jochim, 1939). The isolated fibrillating heart of dogs gives *coronary dilatation* on perfusion with epinephrine (sometimes preceded by slight constriction); acetylcholine and physostigmine (antagonized by atropine); $CaCl_2$, NaCl, KCl below $1\frac{2}{3}$ of blood concentration; nitrite and glyceryl trinitrate; histamine; caffeine, aminophylline and other xanthines. *Coronary constriction* results from pitressin, atropine, ergotamine, piperodimethylbenzodioxane, KCl above $1\frac{2}{3}$ of blood concentration (Katz and Lindner, 1939). The coronary flow, however, is complicated by the effect on the cardiac contractions, cardiac output and aortic pressure, and the transfer to the intact circulation is not always clear (Wiggers).

Cerebral vessels respond feebly to autonomic drugs. The cerebral blood flow is therefore determined chiefly by the arterial pressure. In cats and rabbits it is *increased* by vasodilators, carbon dioxide (local concentration), nitrite, mecholyl, caffeine and ether, as well as by vasoconstrictors, epinephrine, pitressin and ephedrine. Histamine *decreases* the flow; ergotamine generally does so (J. P. Hendrix and Schmidt, 1938).

Portal vessels have strong constrictor reactions, the portal blood flow being decreased (in dogs) by epinephrine, choline esters, histamine and digitalis. It was increased by amyl nitrite (L. N. Katz and Rodbart, 1937).

Spleen.—The spongy blood spaces, which may hold a tenth of the entire blood, are largely outside of the active circulation. For instance, the concentration of carbon monoxide and methemoglobin, in poisoning, is less in the splenic than in the circulating blood. Much of the splenic blood can be versed into the general circulation by contraction of the trabecular muscles (Barcroft and Stephens, 1927); a single contraction may increase the total blood volume by 2.6 to 5.6 per cent (Cruikshank). Splenic contraction is stimulated by epinephrine (Suzuki, 1927), and also by ephedrine, the choline esters, physostigmine, pilocarpine, pituitrin, chloroform inhalation, and by nicotine, the latter partly by increasing the output of epinephrine. Intravenous sodium amytal produces relaxation (J. E. Davis, 1937; McCrae, 1930). Contraction of the spleen increases the blood volume and the erythrocyte count, and causes complex changes in the leukocyte picture (Menkin, 1929). The spleen acts as a mechanical elastic reservoir of blood volume. It also has complex and obscure relations to *blood destruction and regeneration of blood corpuscles*. It can be removed with but little disturbance, so that its functions can evidently be carried vicariously by other mechanisms; injection or feeding of extracts ordinarily produces no striking or even very definite effects.

The capillaries tend to follow passively the changes in the arterioles, and are therefore generally constricted by sympathetic, and dilated by parasympathetic, stimulants; and similarly by other arteriolar constrictors (barium, pitressin) and dilators (nitrites). Histamine, peptone, anaphylaxis and inflammatory irritants generally dilate the capillaries directly and increase their permeability. Precipitant agents (astringents) contract and decrease permeability.

P. Rous *et al.*, 1930, believe that the permeability increases toward the venous side of the capillaries. Landis, 1927, found the permeability of dilated capillaries no greater than of the contracted (review, N. L. Hoerr, 1944). Krogh, 1922, believed that the capillary flow is controlled by scattered smooth muscle cells (the Rouget cells), with sympathetic innervation, responding to epinephrine only for a short distance beyond the arterioles, but controlled especially by pitressin, which he considered a special hormone for the capillaries. Other workers claim that the Rouget cells are not muscular but connective tissue (Michels, 1936). Others again assert that mechanical and electrical and sympathetic nerve stimulation causes the endothelial nuclei to bulge into the lumen of the capillaries, so as to occlude them completely (M. E. Field, 1935; Sanders, Ebert and Florey, 1940). *A priori* it seems probable that the endothelial cells themselves may contract, somewhat analogous to the chromatophores; evidence for this was brought by J. B. Rogers, 1935, and E. R. Clark and Clark, 1935. Fulton and Lutz, 1940, conclude that there is neither endothelial contraction, nor nuclear swelling, nor endothelial valves, but that the regulation is performed by the smooth muscle cells at the end of the capillary. Capillary permeability may be tested in rats by intravenous injection of 1 cc. of 1 per cent trypan blue in 6 per cent dextrose and killing the animal in two hours (Spagnol, 1928).

Carotid Sinus and Aortic Reflexes.—Increase of intracarotid pressure lowers the general blood pressure, slowing the heart by increasing the normal tone of the cardio-inhibitory center and by depressing the tone of the vasoconstrictor center. It also depresses the respiratory center and produces reflex depressions and inhibitions, resulting in miosis, diminished discharge of epinephrine, decrease of metabolism and of muscular activity. These effects are in the general direction of parasympathetic stimulation. Lowering of the intracarotid pressure produces the reverse effects, resembling orthosympathetic stimulation. They arise reflexly by the mechanical stretching or relaxing of receptive endings scattered about in the arterial wall of the carotid sinus, the ampulla located at the junction of the external and internal carotid artery. Denervation or cocainization of the sinus produces the hypotensive reactions, tachycardia, rise of pressure, hyperpnea, etc. These reflexes are called into play by pharmacologic agents which raise or lower the general blood pressure; and the autonomic responses may be blocked by drugs which paralyze the autonomic ganglia, or the parasympathetic and sympathetic endings (nicotine, atropine, ergotamine). The intercarotid glomus and the aortic body contain another receptive organ, also rich in nerves, which mediates similar reflexes in response to a variety of chemical agents: Increase of respiration and the orthoparasympathetic group of reactions are produced in this way by hypercapnia, anoxia, acidosis, cyanide, sulfide, nicotine, lobeline, etc., and the vasomotor and respiratory stimulation by these drugs is largely due to this reflex (Heymans *et al.*, 1933; A. Verdonk, 1941; Bouchaert and Pannier, 1942; review, C. F. Schmidt and Comroe, 1940).

Clinically, the carotid sinus reflex is elicited by digital compression of the carotid ampulla (originally described as "vagus-compression reflex" by Tschermak, 1868), resulting in cardiac inhibition, etc. The reverse effects are produced by digital compression of the common carotid artery. *The effects of drugs on the cardio-inhibitory reflex are described* by Nathanson, 1933: Atropine abolishes the response. Epinephrine also prevents cardiac arrest by inducing idioventricular rhythm. Digitalization prolonged the duration of the arrest. Calcium gluconate and therapeutic doses of caffeine had no effect. The *course* of the nerves from the intercarotid glomus and ampulla is through the pericarotid plexus and the nerve of Hering or Castro to the glossopharyngeal nerve trunk. The vasoconstrictor response is general, *i. e.*, it extends to all vessels with vasoconstrictor innervation. *Hyperventilation* decreases the respiratory stimulation of the carotid body by nicotine and cyanide (Larson *et al.*, 1944).

Cardio-Aortic Depressor Nerve.—Receptive endings with functions closely analogous to those of the carotid ampulla are located in the walls of the aortic arch, the subclavian and brachiocephalic arteries and probably in the heart. They help to maintain the normal cardioinhibitory tonus and to moderate the blood pressure. Their stimulation (as also that of the depressor nerve through which they run to the glossopharyngeal nerve) results in fall of blood pressure by inhibition of the vasoconstrictor and reciprocal stimulation of the vasodilator tone; and in slowing of the heart rate, chiefly by stimulation of the vagus, and to a less degree by reciprocal inhibition of the accelerator center. It also decreases the output of epinephrine. Division of the depressor nerve has the opposite effects.

The function of the carotid sinus and cardio-aortic reflexes is to stabilize the circulation of the brain and heart automatically against changes of the general blood pressure or asphyxia. Through the carotid sinus reflex, fall of the general blood pressure results in cardiac acceleration and increased cardiac output, and in vasoconstriction, which diverts a greater proportion of the blood supply to the weakly innervated cerebral and coronary arteries. The aortic and carotid sinus reflexes protect the brain against excessive blood pressure and the heart against excessive resistance; the stimulation of the chemical receptors of the carotid glomus by asphyxia automatically augments the pulmonary ventilation by which asphyxia is ordinarily prevented. The carotid sinus responses are most marked with pressures near to normal. They tend to disappear when the blood pressure rises to 200 or falls to 50 mm. Hg. Below 50 mm., the reactions are reversed.

Reflexes from Other Blood Vessels.—Reflex pressure changes have been described as following the localized injection of irritants, especially acids, into the vessels of various areas (Tournade and Malmejac, 1931): but Heymans *et al.*, 1933, found that the femoral artery responds only to high concentrations which produce intense local contracture of the vessel wall, which would give rise to ordinary pain reflexes.

Melanophore cells of the scales of fish and skin of frogs are typically subject to autonomic drugs, contracting and relaxing much like smooth muscle. Some are controlled by nerves, others by circulating neurohormones (G. H. Parker, 1944). In *fish* this varies with species. In dogfish they are dilated through pituitary hormone, contracted through nerves; in fundulus the control is entirely through antagonistic ortho- and parasympathetic innervation (Parker, 1935). They are contracted by *epinephrine*, and this is reversed by *ergotoxine*. They are relaxed by *atropine* and apparently also by pilocarpine and physostigmine (Barbour and Spaeth, 1917). *Barium chloride* and *guanidine* provoke *rhythmic contractions*, at the regular rate of about once a minute, synchronous for all the melanophores of the scale. This coordination indicates an extracellular action, presumably on the nerve fibers, analogous to the nerve-muscle rhythm which these drugs induce in striped muscle (Veil, Comandon and Fonbrune, 1932). *Frog melanophores* are contracted both by sympathetic (epinephrine, tyramine) and parasympathetic (pilocarpine, acetylcholine) stimulants (Kobayashi, 1928). Pituitary extracts dilate, the active agent being located in the pars intermedia (Geiling). Teague and Noojin, 1938, reported on reactions to an extensive list of drugs. A. O. M. Stoppani, 1942, reports that the color of frogs and toads is not changed by acetylcholine, and believes that their responses are exclusively adrenergic. They are *lightened* by epinephrine, ephedrine, cocaine and calcium chloride; *darkened* by atropine, barium, chloride, caffeine, chloretone, F 933, nicotine, physostigmine, potassium chloride and veratrine. *Denervation* had little effect on the responses. Some of the reactions, such as those to caffeine and nicotine, are mediated through the hypophysis or adrenals.

AUTONOMIC POISONS AND SKELETAL MUSCLE

Skeletal muscles are not "autonomic"; they are entirely passive and do not even have tonus except on direct order of the central nervous system. They respond, however, to cholinergic drugs, and their stimulation is probably mediated by acetylcholine. Their relation to epinephrine is more obscure.

Acetylcholine Formation in Skeletal Muscle.—Dale, Feldberg and Vogt, 1936, reported the presence of acetylcholine in saline solution perfused through voluntary muscle when its motor nerve is stimulated, or on direct stimulation of the muscle, and also after curare, but not after complete fatigue or after degeneration of the divided nerve. From this it appears that acetylcholine is formed in the myoneural junction as chemical mediator of the nerve impulse. It was questioned whether the rapidity of contraction and relaxation of skeletal muscle would leave time for the chemical mediation of synaptic transmission (Bremer, 1934), but this doubt appears resolved by the demonstration that the concentration of choline acetylase in the synaptic region is "many thousand times as high as in the muscle tissue" (Marnay and Nachmansohn, 1938). However, the nerve-free part of the frog sartorius contains as much acetylcholine precursor as the neural region (N. O. Abdon, 1945).

Injection of acetylcholine solution into the artery of exsanguinated skeletal muscle (so that it may reach all the fibers suddenly and at once) produces a strong muscular twitch, similar to that of nerve stimulation. This is prevented by curare, as is the response to nerve stimulation; and by nicotine, as are ganglionar responses. The single twitch requires prompt destruction of the acetylcholine by acetylase; if the muscle was treated with physostigmine, the acetylcholine produces a tetanus (Dale, Feldberg, and Vogt, 1936).

If the whole muscle is immersed in the solution so that the acetylcholine reaches the fibers gradually, the effects are somewhat modified, and are essentially identical with those of physostigmine, nicotine, guanidine and barium, with quantitative differences that tend to disappear by varying the dosage: (*a*) the lowest effective concentrations produce fibrillary twitchings; with increasing doses these pass to clonic contractions, tonus contractures, and finally into curare-like depression. (*b*) With all, the action is strongest at the site of the end plate (Langley). This might mean that the receptive mechanism is concentrated at this place, or merely that the permeability of the cell wall at this place is more favorable to the penetration of the drugs or ions. The "hypolemma" membrane is indeed thinnest in the neural region. After degeneration has been completed, this preferential action of nicotine becomes less marked, and at that time the sarcolemma has grown over the denervated end plate. (*c*) All continue effective for some time after the division of the nerve endings; indeed, the sensitivity is increased for a time, as in other nerve degenerations. Most and probably all become less and less effective when the nerve has completely degenerated, presumably because the receptive mechanism, and eventually the muscle fibers as a whole, deteriorate when they are no longer used. (*d*) All are antagonized, though to a varying degree, by curare, atropine and especially l-scopolamine, and the local anesthetic group. Atropine is more effective against drugs than against nerve stimulation; a difference it frequently exhibits in strictly parasympathetic reactions, which is again merely quantitative, for sufficiently large doses of atropine block the response of striped muscle to nerve stimulation (Haffner, 1918).

Choline and its esters produce a brief twitch in some muscles, a prolonged but reversible contracture in others. In *mammals*, all fetal muscles respond by the prolonged contracture until voluntary control develops. In adult mammals only the diaphragm gives the prolonged contracture, but this reappears in the other muscles if their motor nerve is divided and degenerates; *i. e.*, the long-contracture response disappears when the muscle becomes voluntary and reappears when it is rendered involuntary (review, H. Freund, 1932).

Nicotine produces either fibrillary contraction or tonus and with large doses a curare action. *Guanidine and barium* cause coordinated rhythmical twitching of muscle. The action does not occur after degeneration of the nerves (Veil *et al.*, 1932).

Rhythmic Twitching of Mammalian Skeletal Muscle.—The spontaneous twitching under physostigmine results from repetitive discharges of the motor nerve endings (Feng and Li, 1941). Single nerve volleys evoke a regular series of contraction spikes which undergo a logarithmic decrement (G. L. Brown and Harvey, 1941). *Denervation* renders muscle much more susceptible to fibrillation by acetylcholine, and somewhat more to potassium; both are inhibited by quinidine (Magladery and Solandt, 1942). Transmission fatigue and contraction fatigue are independent phenomena (S. E. Steiman, 1943). Denervation also tends to produce spontaneous fibrillation. Electric potential changes show that these contractions originate solely in the end plate zone, and are arrested if this is excised (Hayes and Woolsey, 1942). S. W. Kuffler, 1943, confirmed on single nerve-muscle fibers of frog's sartorius that acetylcholine, nicotine and caffeine depolarize the muscle membrane where the end plates are located, but not at other regions. Curare opposes the depolarization; nerve degeneration increases it.

Ameboid movements of the end plates are described by E. J. Carey, 1942. The hypolemmal branches expand when the muscle fiber contracts and retract when the fiber relaxes. Physostigmine and acetylcholine expand, curare and quinine retract. Carey, 1944, conceives that neuromuscular transmission is blocked through this ameboid retraction and the formation of a circumscribed precipitation membrane composed on Kühne's granules. Injection of dilute lactic acid into rats causes sudden destruction of most of the motor end plates (Carey and Massopust, 1944).

Epinephrine is reported to diminish the onset of fatigue, even in perfused muscle, where it diminishes the blood flow. The improvement is not seen on direct stimulation of fully curarized muscle, so that it must be due to improved synaptic transmission of nerve impulses. Similar augmentation is produced by ephedrine, tyramine, synephrine and cocaine and also by ergotoxine and posterior pituitary (Bulbring and Burn, 1940). *Ephedrine* is used clinically in muscular dystrophies, but always with other measures, and it is not established that it has any effect.

Sympathetic Innervation of Striped Muscle.—Sympathetic fibers have been traced to the striped muscle fibers, especially by the degeneration method (Dusser de Barenne and co-workers, 1919). Their functional significance is still obscure. Dusser de Barenne (1916) and S. Cobb (1918) showed that division of the sympathetic supply has essentially no effect on the tonus. The sympathetic innervation was then credited with the regulation of the metabolism of the muscle, but Langley pointed out the difficulty of distinguishing a sympathetic innervation of the muscles from a sympathetic innervation of the blood vessels in the muscles. This also vitiates the observation that sympathetic stimulation tends to increase the amplitude of muscular contraction, especially when the muscle is fatigued. Epinephrine does not affect the contraction or tonus in excised muscle (Takayasa, 1916). On the other hand, epinephrine increases the carbon dioxide production, even in excised muscle (Martin and Armitstead, 1922), and also creatine formation (Riesser, 1916). This indicates that the sympathetic innervation may be concerned with functions of muscle in general metabolism; perhaps in heat regulation.

Reactions of Invertebrate Muscle.—The response of the striated muscle resembles closely that of the vertebrates; even the smooth muscle of invertebrates reacts to drugs much like striated vertebrate muscle (O. Riener, 1933). The *central reactions of insects* to autonomic poisons rather resemble those of vertebrate ganglia: When injected into the heart of mantids or roaches, strychnine produces pure depression; pilocarpine and physostigmine, great excitement which is prevented by atropine; acetylcholine has no detectable effect. The electric activity of the isolated ventral nerve cord of cockroaches shows similar changes (K. D. Roeder and Roeder, 1939). The response of various organs in *Daphnia* differs in many respects from those of vertebrates (Sollmann and Webb, 1941).

The nervous system of the invertebrates is reviewed by C. L. Prosser, 1946; that of the arthropods by J. H. Welsh and Schallek, 1946. Cholinergic systems are widespread above coelenterates.

Protozoa.—Papaverine produces marked swelling; histamine, shrinkage. The effects begin at the vacuoles and extend to the protoplasm. This has been proposed as a model of the effects on muscle (H. S. Hopkins, 1922), but the analogy is yet to be established.

Autonomic Poisons on White Cells.—The proportion of these cells is changed, the significance being obscure. Pilocarpine and choline increase, atropine diminishes the eosinophils and lymphocytes. Epinephrine increases the lymphocytes but diminishes the eosinophils. Histamine also diminishes the eosinophils (Port and Brunow, 1914).

Yeast formation is affected by some of the autonomic drugs. It is accelerated by low and inhibited by higher concentrations of atropine, quinine, and basic dyes (methylene blue). Pilocarpine and cocaine inhibit in low and accelerate in higher concentrations (Somoggi, 1916).

THE RESPONSE OF SECRETIONS TO AUTONOMIC POISONS

Pilocarpine stimulates and atropine arrests the secretions controlled by a central parasympathetic innervation: saliva, buccal and bronchial mucus, gastric and pancreatic juice. The sweat glands respond to cholinergic drugs, although their innervation is chiefly if not solely orthosympathetic (review, C. W. Darrow, 1943). Other parasympathetic stimulants are much less effective than pilocarpine. The salivary and sweat glands can also be caused to secrete by stimulating their sympathetic nerves; but epinephrine does not evoke secretion, perhaps because it produces too much vasoconstriction. It is an effective secretory stimulant for the sympathetically innervated skin glands of the toad (Wastl, 1921).

The pancreatic and gastric secretion may also be stimulated by histamine and peptone, and by specialized "hormones," such as secretin. These are not antagonized by atropine, and presumably act on a "responsive" mechanism of the gland cell.

Similar chemical hormones probably affect the regulation of the secretions that are not under nervous control and are not responsive to pilocarpine and atropine; *i. e.*, the urine, bile, milk, the secretions of the oviduct (Riddle and King, 1921), the cerebrospinal fluid (Becht and Gunnar, 1921) and the whole series of "internal secretions."

Oral and pharyngeal mucus secretion is greatly increased by pilocarpine, arrested by atropine. *Epinephrine* has no effect or causes a slight increase (stimulation of the cervical sympathetic increases). *Morphine* increases the mucus during nausea and tends to decrease it during narcosis (M. F. Montgomery, 1934, dog).

The **fluid secretion of the respiratory tract** is increased by parasympathetic stimulants (E. M. Boyd and Lapp, 1946).

Salivary secretion is increased by *pilocarpine* and *reflexly* by acids and ether. It is arrested by *atropine* (also by *morphine*, acting centrally). The response to *sympathetic* stimulation varies in different animals. In dogs, it provokes a flow of thick, mucilaginous saliva from the submaxillary and none from the parotid gland; in cats, it gives a profuse mucilaginous flow from the submaxillary and a scanty, thick secretion from the parotid. Histologic data indicate that the demilune cells of cat's submaxillary gland are innervated by the orthosympathetic, the mucus cell exclusively by the parasympathetic (Rawlinson, 1936). *The quantitative antagonism of atropine and pilocarpine on salivary secretion* was investigated by Cushny, 1915, on dogs with salivary fistula. The ratio remained the same (about 1 part of atropine to 9.5 of pilocarpine) whether the two drugs were injected simultaneously or some time apart, and it remained unaltered whatever total dose was injected.

Gastric Secretion.—The peptic cells, which secrete the ferments, the parietal cells, which secrete acid, and the mucus cells may function independently, but all are excited by *parasympathetic stimulation* through the vagus, *pilocarpine* or *choline* and its esters. The increase concerns chiefly the enzymes and mucus (Vineberg and Babkin, 1931). The fluid is not greatly increased by choline in the empty stomach, but the flow in response to test meals is markedly increased (MacIntosh and Krueger, 1938). *Atropine* abolishes the secretory response to parasympathetic stimulation and to a meal, but only partly the response to histamine (J. Gray, 1937). *Histamine*, which is used as a test of achlorhydria, increases the flow, the acid and the inorganic constituents, but not the enzymes or mucus (Vineberg and Babkin, 1931). It stimulates only the parietal cells. The *Brunner glands of the duodenum*, which probably secrete chiefly mucin, are stimulated by acetylcholine, and by a hormone. *Mucus secretion of the colon and cecum* is stimulated by local irritation with mustard oil or acids, not by histamine, peptone or acetylcholine (Florey and Webb, 1931).

The **pancreatic juice** is controlled chiefly by secretin; but it is increased by pilocarpine and by vagus stimulation and is inhibited by sympathetic stimulation. The insulin output is probably regulated directly by the blood sugar level.

Prostatic secretion responds to drugs somewhat like sweat and submaxillary saliva. It is increased by pilocarpine, acetylcholine, epinephrine and nicotine. Histamine and yohimbine have no effect. Atropine and ergotamine antagonize pilocarpine (Farrell and Lyman, 1937).

Milk Secretion.—This is started and regulated by the sex hormones. Takahashi, 1927, reported that it is increased in goats by both pilocarpine and epinephrine, but the response is uncertain.

◆

ATROPINE

Atropine and other closely related alkaloids (hyoscyamine, scopolamine, etc.) produce a variety of peripheral and central effects: (1) complete paralysis of the peripheral distribution of the parasympathetic (craniosacral autonomic) nerves (oculomotor, secretory, bronchial musculature, cardiac and intestinal vagus, uterus, etc.); (2) consequently, antagonism to pilocarpine, choline and its esters, physostigmine, muscarine, etc.; (3) excitation and then paralysis of certain cerebral and medullary centers; (4) slight peripheral sensory paralysis, on local application; (5) slight stimulation and, in large doses, subsequent depression of smooth and cardiac muscle and other cells.

Mechanism of Parasympathetic Paralysis.—Atropine antagonizes acetylcholine, and since this stimulates after nerve degeneration, the action of atropine appears to be on the receptive mechanism. It does not prevent the formation of acetylcholine on nerve stimulation, but prevents it from acting on the cell. Atropine paralyzes also a few augmentory and inhibitory sympathetic nerves (uterus and sweat glands; Cushny, 1910).

The *dosage of atropine required to paralyze parasympathetic response* varies widely for different organs; for instance, V. E. Henderson, 1923, reports the following as necessary to block response to electric stimulation of the nerves (mg. per Kg.): salivary secretion (chorda), 0.025 to 0.15; cardiac vagus, 0.07 to 0.7; pyloric sphincter, small intestines, chorda dilator, to 5 mg.; urinary bladder, more than 20 mg. Very much smaller doses prevent stimulation by pilocarpine.

Occurrence.—Atropine occurs in a number of plants (*Belladonna, Stramonium, Hyoscyamus, Scopola, Mandragora, Duboisia,* etc.) belonging to the order Solanaceae (the potato family). These also contain other alkaloids (hyoscyamine, scopolamine, etc.) closely related to atropine in structure and in action. The alkaloids, as first isolated, were mixtures; consequently, their properties appeared to vary with the origin, and these mixtures were given specific names (daturine, duboisine, etc.). The pretended difference between scopolamine and "hyoscine" is a survival of this tradition.

Historical.—The first indubitable notice of *belladonna* occurs in 1504, but it then came quickly into use for poisoning and cosmetic purposes. The name Atropos, which Linné gave to the plant, is from the oldest of the Three Fates, who cuts the thread of life. Belladonna comes from the Italian "handsome woman," as it was used to give luster to the eyes. On account of the slow course and the obscure symptoms, belladonna was a favorite with professional poisoners in the Middle Ages, and this abuse in regard to several species of Datura (Stramonium) has existed in India since remote ages. The name itself is Sanskrit (Dhatoora). Belladonna seems to have been first introduced into practice as an anodyne about 1860. *Hyoscyamus* was mentioned by Dioscorides in the first century and has been used continuously in folk medicine. It was introduced into practice by Stoerck in the middle of the eighteenth century. He also introduced *Stramonium. Mandragora* (Mandrake) was the subject of interesting medieval myths. The "herbarium" of Apuleius (eleventh century) cites its use externally for headache and insomnia and internally for mania.

Chemical Structure and Relations.—These alkaloids are ester-like combinations of certain bases with organic acids of the aromatic series. *Atropine* is the tropeic acid ester of a base, tropine, and is isomeric with *hyoscyamine;* hyoscyamine is levorotatory, while atropine is racemic. The esters of tropine are called *tropeines. Homatropine* is the mandelic ester of tropine; and other tropeines occur naturally or may be prepared synthetically. Tropine itself is related to ecgonine, the basic constituent of cocaine. The *osceines* are analogous esters of the base oscine. The tropeic acid ester constitutes the important alkaloid scopolamine or hyoscine. This also occurs in isomeric forms: *atroscine* (racemic, corresponding to atropine), and *scopolamine* proper (levorotatory, corresponding to hyoscyamine). Atropine and atroscine are the more stable products: alkalis and many other agents convert hyoscyamine into atropine, scopolamine and atroscine.

Belladonnine and *atropamine* are isomeric alkaloids (belladonnic acid tropeines), differing from atropine by the absence of a molecule of H_2O. They are present in the plants in small amount, and it is possible that they are formed only during the extraction.

Constitution and Action.—The relation between these was investigated by Cushny, 1920, using as criterion the antagonism of the pilocarpine salivation. The atropine effect is absent from tropine itself, but is produced by many of its compounds, especially those with the benzene nucleus. The *asymmetric carbon* is very important. The l-hyoscyamine is forty times more active than the d-hyoscyamine, but even this is more active than the nearest homologues that do not contain asymmetric carbon. This is not indispensable, however, for some activity exists in tropines without asymmetric carbon and without hydroxyls. The parasympathetic paralyzing potency is greatly diminished by *hydrolysis* into tropine and tropeic acid (Exler and Van Nieker, 1929). Both are involved in the action. The sulfuric ester of atropine is nearly devoid of peripheral actions, while the central effects, especially the respiratory stimulation, are preserved. Scopolamine-sulfuric ester does not share this respiratory action (Trendelenburg, 1913).

Other esters of tropine have been investigated by Rav, 1934. *Other esters of tropic acid* are all more or less paralyzant to parasympathetic stimulation, and antagonize intestinal stimulation by barium. The levo isomers are considerably more potent than the dextro, as is the case with atropine (Fromherz). *Apo-atropine* is formed along with atropine when hyoscyamine is treated with alkali. It acts directly on smooth muscle. It is five times more potent than atropine on the intestines, but acts weakly on the pupils and on salivation. It has a central excitant action. It is twenty times more toxic to mice than is atropine or hyoscyamine (H. Kreitmair and Wolfer, 1938; Sasa, 1939).

Distribution of Alkaloids.—*Belladonna and Stramonium* contain mainly atropine and hyoscyamine; one or the other alkaloid may predominate. The hyoscyamine is the most widely distributed of these alkaloids and is especially abundant in young parts of the plants, whereas older parts contain more atropine. It appears that the hyoscyamine is the original alkaloid, and is partly transformed into atropine in the plant itself and also during extractions. Stoll found that fresh belladonna leaves contain only l-hyoscyamine. The dried plant also contains small traces of scopolamine and atroscine, but the latter alkaloids are relatively more abundant in *Hyoscyamus* and *Scopola*, taking the principal part in the actions of these plants. The distribution and variation of the aklaloids in individual plants, as studied by Sievers, 1913 to 1915, suggest improving the alkaloidal content by selective breeding. *Discrepancies between the chemical and biological assays* of belladonna and stramonium are discussed by Watson, Heard and James, 1941.

Actions on the Eye.—Atropine dilates the pupil (mydriasis) and renders it insensitive to light. It also paralyzes accommodation (cycloplegia), the lens being adjusted for far vision. These actions are peripheral and consist in paralysis of the oculomotor endings. The intra-ocular tension in glaucoma is increased, the cycloplegia relaxing the muscle fibers which ordinarily draw open the lymphatic drainage canals of the ciliary zone. The atropine mydriasis and cycloplegia are persistent; the mydriasis may last for several days. The ocular actions are produced in varying degree by all the atropinoid alkaloids. The atropine effects may be removed by drugs which stimulate the oculomotor reception (pilocarpine, physostigmine, choline esters, muscarine), and *vice versa.* The mydriatic effect of atropine is generally assisted by *reciprocal (central) stimulation of the sympathetic innervation,* so that the atropinized pupil contracts somewhat if the sympathetic innervation is severed. Atropine does not stimulate the sympathetic directly.

Localization of the Atropine Mydriasis.—Atropine dilates the pupil on local, as well as on systemic, application, The mydriasis remains confined to the eye, and even to that side of the eye to which it is applied. The dilatation is produced in the excised eye, and even in the isolated iris. The action must therefore be peripheral.

Direct Action on the Iris Muscle and Ciliary Ganglia.—The statement that the muscular fibers are not affected by atropine must be limited to moderate doses. High concentrations produce temporary miosis, attributed to direct stimulation of the muscle, followed by paralysis. Direct application of strong solutions to the ciliary ganglion also depresses this structure. The mydriatic effect on enucleated eyes of frogs is reported to be stronger for atropine sulfate than for the citrate or propionate (Régnier and Quevauviller, 1939). The *iris of birds* consists of striped muscle and is not dilated by atropine, but by curare.

Cycloplegia.—The ciliary muscles, situated at the junction of the choroid and the cornea, consist of radial and circular fibers, the former predominating. The contraction in both planes narrows the ring of attachment of the suspensory ligament of the lens, thereby relaxing the tension on this ligament, thus permitting the anterior surface of the lens to become more convex, *i. e.*, to accommodate for near vision. The ciliary muscles are innervated by the oculomotor, and are under more or less tone. Their paralysis by atropine fixes the lens for far vision; and their spasm by pilocarpine or physostigmine, for near vision. The derivatives of atropine are all cycloplegics. The sympathetic mydriatics, cocaine and some synthetic bases, epinephrine and ephedrine have little effect on accommodation. They may reduce its range, but do not change the static tonus of the ciliary muscle (Hartgraves and Kronfeld, 1931).

Changes in Intra-Ocular Tension.—All mydriatics tend to increase intra-ocular tension in glaucoma, although not in the same degree, Conversely, the tension is lowered by miotics. Neither has much effect on the normal intra-ocular tension (Luebs, 1913; Myashita, 1913).

Mechanism of the Change in Tension.—It is believed that the rise of pressure in mydriasis is produced mainly by lessened filtration of the aqueous humor into the venous sinuses of the channels of Fontana and canal of Schlemm. These lie in the angle of attachment of the iris and would be compressed by the relaxation of the ciliary muscle and by the crowding back of the iris. Miosis would have the opposite effect (especially in glaucoma; in the normal eye miotics lower the pressure very little). The intra-ocular tension is also influenced by the blood pressure in the vessels of the iris (Leber), and would be lowered whenever these are ischemic through fall of the general blood pressure (relatively little influence; Kochmann and Roemer, 1914), or through local vasoconstriction. The vasoconstricting cocaine, therefore, generally lowers intra-ocular tension, although it produces mydriasis; and it is claimed that atropine also tends to lower the pressure in the *normal* eye. Exceptionally, however, glaucoma attacks have been reported after cocaine, phenacaine, and even after epinephrine (Gifford, 1916).

Glaucoma.—The phenomena of this serious eye disease depend mainly upon excessive intra-ocular tension presumably due to blocked drainage (Schoenberg, 1913). It is therefore treated by miotics (see physostigmine), and contraindicates the employment of mydriatics. If their use is indispensable, cocaine and ephedrine should be chosen; and if cycloplegia is necessary, the briefly acting homatropine would be preferred to atropine.

Clinical Application of Atropine to the Eye.—Atropine is utilized mainly for paralyzing the ciliary muscle to facilitate ophthalmoscopic examination; and in the treatment of iritis. For *diagnostic work*, the persistent cycloplegia is often objectionable, but in other cases the enforced rest of the eye may be desirable. The less persistent homatropine may be substituted. This is less liable to provoke glaucoma, but in that disease it should also be used as dilute as possible (1 or 2 per cent), and followed by physostigmine, 0.2 per cent, a drop three times daily until the pupil and accommodation have returned to normal (Gifford, 1916). In *iritis*, atropine mydriasis is used to secure rest, to prevent adhesions of the iris to the lens, or break them if already formed, and to effect assumed favorable changes in the circulation of the iris. The more prolonged action of atropine causes it to be preferred for this purpose.

Administration to Eye.—The atropine is applied locally, by dropping an aqueous solution of the sulfate, or an oily solution of the free alkaloid, on the cornea; or by placing impregnated gelatin discs (*Lamellae Atropinae* B.P., $\frac{1}{5000}$ grain) in the conjunctival sac. Watery solutions tend to flow into the lacrimal duct, thereby lessening the local action, and tending to systemic poisoning. To avoid this, a single drop of 1 per cent solution should be applied at a time, and the lacrimal sac should be compressed with the finger. For continued use, in iritis, greater dilutions may be employed, down to $\frac{1}{10}$ per cent (even 1:100,000 is somewhat effective).

Duration of Action of Atropine.—With a single drop of 1 per cent atropine solution, the mydriasis reaches its maximum in about twenty-five minutes, the cycloplegia in about two hours. The cycloplegia disappears in two or three days (seven to nine days if the application has been continuous); the mydriasis endures even longer, ten to twelve days. The persistence of the action is due to the slow exchange of the intra-ocular fluids. The duration increases with the dosage, and on intravenous injection (Koppanyi and Lieberson, 1930).

Side Actions.—Besides the increase of tension, atropine causes photophobia (because of the irresponsive pupil), and micropia, from the loss of accommodation. In sensitive individuals, it produces some conjunctivitis, and rarely edema of the eyelids. If it is used carelessly, it may give rise to systemic poisoning, headache, dryness of the mouth, palpitation, etc. Chronic poisoning may occur in this way (Tyrrell, 1906). If atropine causes local irritation, scopolamine should be substituted, since this may be used in one-fifth the concentration.

Substitutes for atropine fall into two classes: (1) Those which produce mydriasis without cycloplegia (eucatropine or euphthalmine; ephedrine); and (2) those which produce both mydriasis and cycloplegia (atropine, hyoscyamine, scopolamine, eumydrine and homatropine—in the order of the persistence of the cycloplegia). Hyoscyamine is effective in about one-half the concentration, scopolamine in one-fifth the concentration, of atropine.

Quantitative measurements of the relative efficiency of mydriatics and miotics, alone and combined, are given by Joachimoglu, 1915.

The following table shows the strength of solutions

Drug	Percentage used	Mydriasis		Cycloplegia	
		Action complete, hours	Recovery complete, days	Paralysis complete, hours	Recovery complete, days
Atropine	1	$\frac{1}{2}$	5 to 7	2	3 to 4
Scopolamine	$\frac{1}{5}$	$\frac{1}{2}$	5	1	3
Eumydrine	1 to 5	$\frac{1}{2}$	2	1	2
Homatropine	2	$\frac{1}{2}$	1 to $\frac{1}{2}$	1	1
Eucatropine	5 to 10	1	1		

usually employed for ophthalmoscopic examinations, and the ordinary duration of their actions.

***Homatropine Hydrobromide,** U.S.P., the mandelic ester of tropine. Freely sol. in water (1:6), sol. in alc. (1:40). Instilled as 1 to 2 per cent solution. Dose, 0.5 to 1 mg., $\frac{1}{120}$ to $\frac{1}{60}$ grain. Its systemic actions are similar to those of atropine, probably somewhat less toxic. Coma with recovery occurred after the hypodermic injection of 40 mg. Homatropine affects the parasympathetic, for instance the vagus, much less than atropine; or rather, requires five to ten times as high a dosage to paralyze (Zulik, 1915). Homatropine also dilates the conjunctival vessels and on injection lowers blood pressure. Macht, 1922, attributed the actions of homatropine to the *mandelic acid* part of the ester, rather than to the tropine.

Eumydrine (Methylatropine Nitrate). Readily sol. in water. It agrees closely with atropine in systemic actions and may be substituted for it, in the same dosage; in eye, $\frac{1}{2}$ per cent. Its toxicity is about one-fiftieth and its mydriatic strength one-tenth that of atropine. Cushny, 1920, found it one and one-half times more active than atropine in the salivary pilocarpine antagonism. Continued use may lead to some tolerance.

Eucatropine Hydrochloride, U.S.P. (*Euphthalmine*), is a mandelic ester of a base similar to beta-eucaine. It is useful for ophthalmic examinations: Instillation of two or three drops of a 2 per cent solution produces wide dilatation of the pupil within half an hour. It does not produce anesthesia, irritation or cycloplegia. It does not raise intra-ocular pressure in normal individuals, but it may precipitate glaucoma attacks in patients disposed to these. The mydriasis disappears more rapidly than with homatropine. The systemic effects resemble those of atropine. It is readily soluble in water and may be used to 10 per cent.

Use as "Antispasmodic."—The atropine-containing drugs, belladonna, hyoscyamine and stramonium, have long been used against spasm of smooth muscle, ranging from asthma to the various "colics." They are highly successful in the few cases where the spasm is due to parasympathetic stimulation; their efficiency against other forms of stimulation is limited.

Several derivatives of atropine have been introduced as antispasmodics, with the claimed advantage of less side actions on other functions: *Novatropine* (*Novatrin*), N.N.R., the methylbromide of homatropine, is used especially against gastro-intestinal spasm and hyperchlohydria. It is less potent and less toxic than atropine. It is marketed in tablets of 2.5 mg. ($\frac{1}{24}$ grain). Dosage, one or two tablets three times daily before meals. *Syntropan,* N.N.R., the phosphate of the tropic acid ester of diethylaminodimethyl propanol, is used as antispasmodic, especially against intestinal colic and dysmenorrhea. Compared with atropine, it produces greater decrease of gastric and intestinal tonus and less dryness, mydriasis and tachycardia (B. B. Clark, Shires *et al.*, 1939). It is marketed in tablets of 50 mg. ($_{6}$ grain) and in 1 cc. ampuls of 10 mg. Dose, 50 mg. orally and 10 mg. hypodermically, three or four times per day.

The structural formulas and relations of synthetic "antispasmodic" chemicals are tabulated by R. R. Buetner, 1945.

Bronchial Muscles and Glands.—Atropine paralyzes the innervation of these structures, and thereby dilates and dries the bronchial tubes. The dilatation is obtained in excised rings of bronchial musculature (Trendelenburg, 1912), and is therefore peripheral. It is effective not only against parasympathetic stimulation (mecholyl, etc.) but also against muscular stimulants (histamine, barium) and anaphylactic spasm (Barlow and Beams, 1932; Sollmann and Gilbert, 1937).

Therapeutic Use against Asthma.—Bronchial asthma involves bronchial spasm, against which atropine should be useful; but it generally also involves acute edema of the mucosa and chronic catarrhal infiltration. The efficiency of atropine is therefore much more limited than in experimental spasms, although it sometimes gives striking relief. Atropine has been largely displaced by the generally more effective epinephrine, but it may be employed as adjuvant. Atropine ($\frac{1}{2}$ to 1 mg., $\frac{1}{120}$ to $\frac{1}{60}$ grain) or the drugs containing it may be administered by any channel.

Inhalation is most effective since it brings the drug directly to the site of its action. *Asthma powders* consist of atropine-containing drugs, mixed with sufficient saltpeter to insure their combustion; *e. g.*, Powdered Stramonium, 3 Gm.; Lobelia, 1; Anise, 2; Potas. Nitrate, 2. This dose is burned on a plate and the smoke inhaled. Stramonium cigarettes are also used; the smoke of 1 to 1.25 Gm. of stramonium contains 0.3 to 0.5 mg. of atropine (Guenther, 1911).

Biliary and Renal Colic.—Atropine paralyzes the innervation of the smooth muscle of the bile ducts and ureters, and therefore relaxes the painful and obstructive spasm which results from the passage of calculi through these tubes. The vagus paralysis is useful by preventing the dangerous cardiac reflex which sometimes occurs. The atropine, 1 mg., $\frac{1}{60}$ grain, is given hypodermically, usually combined with morphine, 15 mg., $\frac{1}{4}$ grain.

Gallbladder.—This may be relaxed (Lieb and McWhorter, 1915); but not by ordinary therapeutic doses (Macht, 1917).

Excised Ureter.—Small doses of atropine may stimulate the tone and peristaltic movements. Stronger solutions (1:10,000) inhibit them, as also the stimulant effects of pilocarpine, physostigmine and choline (Macht, 1916). G. B. Roth, 1917, however, found nicotine, pilocarpine and atropine practically ineffective. Levo hyoscyamine stimulates the contractions and slightly raises the tonus; large doses depress. The dextro inhibits from the start, without stimulation (Macht, 1918).

Urinary Bladder and Incontinence of Urine.—Atropine is employed to relieve incontinence of the urine, due to overaction of the bladder muscle; and retention of urine from overactivity of the vesical sphincter. A. Jacobi advises for children $\frac{1}{2}$ grain of Belladonna Extract at night, increasing if necessary, to flush the cheeks. The actions of atropine on the bladder were investigated by Edmunds and Roth, 1920. It produces primary contraction, then relaxation. It antidotes pilocarpine and physostigmine, but not electric stimulation of the erigentes (confirmed by Henderson, 1922).

Urine Flow.—Cow, 1912 and 1913, finds that atropine has no effect if the urine is collected directly from the pelvis of the kidney, but that it merely modifies the flow through the ureter by lessening its tonus. The suppression of sweat and other secretions might temporarily increase the output of urine.

Uterus.—Clinical doses of scopolamine have little if any effect on the parturient uterus (Dodek, 1932). Larger experimental doses of atropine relax and arrest its nongravid peristaltic movements (Ludwig and Lenz, 1923). It antagonizes pilocarpine, physostigmine and also anaphylactic stimulation, but is not as effective against pituitary extract (Stoland and Sherwood, 1923). *Atropine in dysmenorrhea* was advocated by Novak, 1915, especially in the spasmodic, colic type. The side actions interfere with its use (Litzenberg, 1919). G. Lehmann, 1943, obtained no effect from syntropan and other tropic acid derivatives on excised human uterine muscle, and concludes that any relief of dysmenorrheic pain is probably not due to uterine relaxation.

Intestines.—Atropine relaxes intestinal spasm due to parasympathetic stimulation, but is not very potent against other intestinal stimulation. It has little effect on normal peristalsis, but tends to lower the tonus and slow the propulsion of the intestinal contents. Atropine, 1 mg. ($\frac{1}{60}$ grain), or belladonna extract (15 mg., $\frac{1}{4}$ grain) or tincture (0.5 cc., 8 minims) is sometimes administered in lead and other intestinal *colics*, but they are generally ineffective, as these do not often involve parasympathetic stimulation. They have also been added to *irritant cathartics*, especially aloin, to diminish "griping," but well controlled clinical comparisons indicate that they are inefficient for this purpose.

In unanesthetized dogs with permanent intestinal fistulas of the *small intestines*, moderate doses of atropine caused pronounced and prolonged delay in the propulsion of a soft bolus (Quigley, Highstone and Ivy, 1934). Pressure records show decrease of tonus, without decrease of the amplitude of the rhythmic contractions with moderate doses; but large doses also decreased these. There is mutual antagonism with morphine (C. M. Gruber *et al.*, 1930). The atropine inhibition occurs also after division of the extrinsic intestinal nerves; it may be presumed that it renders the intestinal muscle unresponsive to acetylcholine produced in the muscle independently of extrinsic innervation (Youmans *et al.*, 1943). *Excised intestine of rabbits* is relaxed by atropine. Pilocarpine and other parasympathetic stimulants are antagonized by doses that have no effect on normal intestines (Magnus). If the segment has been extensively soaked in saline solution atropine may produce stimulation instead of depression. This is attributed to loss of parasympathetic tone by the removal of the choline present in the walls of fresh intestine (LeHeux, 1920). *Extreme doses of atropine* (so large that they cannot be brought into action by systemic application, but only locally and in the excised intestine) paralyze successively the ganglion cells, the endings and the muscle, destroying the response to the muscular poisons such as barium. The *optical isomers* of atropine act quantitatively alike on excised intestine (Liljestrand, 1919). The quantitative relation between atropine and pilocarpine has been investigated by van Lidth de Jeude, 1918. *Syntropan* requires fifty times the concentration of atropine to antagonize acetylcholine in excised intestines of dogs. It also antagonizes barium and histamine in a more favorable ratio (B. B. Clark and Shires, 1938).

The natural *colon motility* of dogs is inhibited by atropine (0.03 to 0.05 mg. per Kg.). It prevents the morphine increase of propulsive motility, but not the increase of tonus and nonpropulsive motility (Adler and Ivy, 1940).

Frog's intestine is relaxed by atropine, 1:10,000, especially if the tonus was high. Atropine is somewhat effective against contraction by barium, 1:40,000, and additive to the relaxing effect which pilocarpine has on frog's intestine (G. B. Roth).

Gastric Functions.—Ordinary oral clinical doses of atropine or belladonna have practically no effect on the secretory or motor functions of the stomach. Large doses, especially hypodermic, tend to reduce the volume of gastric secretion, and probably the mucus, but the concentration of the acid may be increased. Pylorospasm and cardiospasm are sometimes relieved if due to vagus stimulation, but not if they are of sympathetic, emotional or ulcerative origin. The minimal effective dose (1 mg., $\frac{1}{60}$ grain, before meals) produces decided side effects, dryness and mydriasis (review, Bastedo, 1936).

Motility of Normal Human Stomach.—Tetelbaum, 1928, reported that pyloric peristalsis is arrested by 0.3 to 0.5 mg. of atropine in the empty stomach, and by 1 mg. after food; Kellermann, 1929, found the emptying time prolonged; but Keefer and Bloomfield, 1926, observed no definite effects on gastric motility after 2 mg. of atropine (with oral administration of 50 cc. of 7 per cent alcohol). Veach, 1937, reports inhibition of gastric motility by intravenous injection of therapeutic doses of atropine and mutual antagonism with the spastic action of morphine. In *cardiospasm* atropine may cause sudden relaxation or it may be ineffective (Barclay, 1915; fluoroscope). It is often used in hyperchlorhydria, especially in acute conditions with severe pain and vomiting (A. Schmidt, 1914). Large doses are employed against *infantile pylorospasm*, 0.05 to 0.15 mg. three to four times a day (Stolte). This produces flushing, but no dangerous effects; it has been given daily to six-week-old infants, for weeks (Ochsenius, 1916). Atropine also inhibits the gastric hypertonicity induced by *insulin hypoglycemia* (Wilder and Schlutz, 1931; dogs) but has little effect on the cardiospasm of vagotomized dogs (G. Lehmann and Knoefel, 1942). *Excised stomach* is relaxed by atropine, and pilocarpine is antagonized (M. Smith, 1918).

Gastric secretion is decreased by moderate therapeutic doses of atropine (Chiari, 1915; Crohn, 1918). Clinically, the decrease involves chiefly the volume, then the acid, and with larger doses also the enzymes (Kellermann, 1929).

With the *histamine test*, atropine decreases markedly the volume of the secretion and the concentration and total output of pepsin, with comparatively slight inhibition of the secretion of acid, so that the concentration of acid rises (Polland, 1930). *With the alcohol test* (50 cc. of 7 per cent alcohol by mouth), atropine (2 mg.) also diminishes the acid secretion less than the volume (Keefer and Bloomfield, 1926). *In dogs*, intramuscular injection of atropine (0.0125 mg. per Kg.) completely inhibits secretion in response to food. Smaller dosage, 0.003 mg. per Kg., diminishes the volume and the peptic activity. The acid concentration is not affected until a dosage is reached that diminishes the volume by 50 to 80 per cent. There is a mutual antagonism toward histamine and gastrin, extending to nearly fatal doses of atropine. With large doses, the atropine and gastrin appear to act directly on the gland cells; smaller doses probably act on some other site (Keeton *et al.*, 1920). *Homatropine* has about a tenth the potency of atropine on gastric secretion (Tennenbaum, 1930).

Antiemetic Action.—Atropine sulfate (1 mg.) or scopolamine hydrobromide (0.5 mg.) (see Index) are probably the most effective agents in *preventing seasickness*, in perhaps half of those who would otherwise succumb. The dosage may be repeated in eight hours.

Eggleston, 1916, found that small doses of atropine (0.01 mg. per Kg.) prevent the emetic action of pilocarpine and nicotine, but not of apomorphine, morphine, ouabain or emetine. It also abolishes the emetic action of magnesium sulfate and diminishes that of intravenous potassium arsenite (Hatcher and French, 1932). The fact that the antiemetic dose is smaller than is required against the peripheral actions of pilocarpine suggests that atropine depresses an emetic center. Hatcher and Weiss, 1923, attribute the antiemetic action to paralysis or blocking of certain afferent paths to the emetic centers, while other paths remain open. S. Wolf, 1943, claims that addition of physostigmine increases the effectiveness of atropine against seasickness, by maintaining the normal gastric tonus and motility which are inhibited in nausea. Others failed to confirm the additional benefit of physostigmine.

Pancreatic Juice.—Atropine suppresses the increase of pancreatic secretion which ordinarily follows stimulation of the vagus or the administration of pilocarpine or choline. Large doses provoke a pancreatic flow in the dog (Modrakowski, 1906); the mechanism of this peculiar action is not understood. Atropine has no direct effect on the flow provoked by secretin (Chiari, 1915), but since it diminishes the secretion of acid in the stomach, it probably lessens the production of secretin indirectly and hence interferes with the physiologic pancreatic secretion. The pancreatic stimulants which are antagonized by atropine yield active juice, whereas those not affected by atropine require the addition of erepsin (Camus and Gley, 1905). Atropine prevents the pancreatic secretory response to vagus stimulation and to fats in acute experiments; but in permanent fistula experiments Savich, 1919, found it ineffective.

Saliva.—The secretion of saliva is suppressed by atropine. This is an unpleasant side effect in the therapeutic use of the drug, but small doses (0.5 mg.) may be employed to allay excessive ptyalism.

The submaxillary gland furnishes a classical object for *localizing the action of atropine*. This suppresses the secretory response to chorda-tympanic stimulation, even when this is applied at the hilus of the gland, *i. e.*, to the postganglionic fibers. The paralysis must therefore be peripheral to these. The cells still respond to sympathetic stimulation, so that the paralysis must be in an intermediary receptive mechanism. This argument, however, involves the assumption that the chorda tympani and the sympathetic act upon the same cells in the salivary gland, which is doubtful (Gaskell, 1916). Large doses of atropine inhibit the response to sympathetic stimulation (Cannon and Cattell, 1916).

In man, Ewing, 1911, found that 0.5 to 1 mg., by mouth, caused marked decrease in the volume of saliva secreted. The percentage of ptyalin fell markedly, but recovered long before the volume or solids had returned to normal.

Vasodilator fibers of the chorda tympani nerve are not affected, so that stimulation of the atropinized nerve still dilates the vessels and produces an increased venous outflow from the gland. (The effects of atropine and pilocarpine on the submaxillary circulation are discussed by Henderson and Loewi, 1905.)

Antagonism.—Atropine completely suppresses nicotine salivation (since this stimulates the ganglion cells); it is mutually antagonistic with pilocarpine, etc., but the atropine action, as usual, tends to be the stronger. The quantitative relations were studied by Cushny, 1915. Atropine is said to suppress *mercurial salivation*, but not the "paralytic secretion" which sets in when the divided nerve degenerates.

Paradoxic Reflex Secretion in Chronic Poisoning.—Abundant reflex secretion of saliva occurs in cats and dogs after repeated injections of atropine and continues for months if the injections are continued. The chorda nerve may or may not be excitable. The sympathetic is excitable (Arima, 1918).

Suppression of mucous secretion may be employed in the hypersecretion of coryza, bronchorrhea, or ether anesthesia. Minimal doses of atropine are used to "abort" incipient colds (0.5 mg., $\frac{1}{120}$ grain or less, in a glass of water, sipped slowly in the course of an hour; Kohnstamm, 1906). The cutaneous vasodilatation may play a part in this abortive action.

Suppression of sweat (anhidrotic action) is one of the earliest actions, and can be secured with small doses (0.3 to 1 mg., $\frac{1}{200}$ to $\frac{1}{60}$ grain, of atropine hypodermically). It is the most effective means of suppressing the nightsweats of phthisis, but the relief is only symptomatic, and scarcely justifies the inconveniences. Atropine decreases the *insensible perspiration* in infants. The decrease averages nearly a fourth, and may be a factor in atropine fever (I. Howe, 1934).

Other Anhidrotics.—Nightsweats may also be suppressed by *scopolamine* or eumydrine. *Agaric acid* arrests sweating by a peripheral action of the sweat glands, but is uncertain. *Camphoric acid* has been employed, but it does not act upon the sweat glands. If it has any effect (which is doubtful) it must be indirect, through improvement of the respiration. *Local measures* are often preferred, especially for local hyperhydrosis: sponging with cold lotions containing alcohol, dilute acids, tannin, salicylic acid, formaldehyde, etc. *Dusting powders* are likewise useful (talcum with 5 per cent of salicylic acid or 10 per cent of boric acid).

Glands that do not have a parasympathetic secretory innervation are not affected directly by atropine. This includes the *kidney*, the *liver* and *all endocrine glands.*

Lacteal Secretion.—Ott and Scott, 1912, confirm Roehrig that this is somewhat diminished by atropine.

Oviduct Secretion of Birds.—Atropine has practically no effect on the secretion of albumen or of shell material (Riddle and Ring, 1921).

The **epinephrine output** is not materially influenced, in cats, by atropine or pilocarpine (G. N. Stewart and Rogoff, 1920).

The **blood sugar level** is somewhat lowered by atropine in normally fed or fasting rabbits and raised by pilocarpine and physostigmine (S. Lang, 1931; Hrubetz, 1936); doses of atropine which produce excitement may thereby raise the blood sugar level (Pitini, 1908; McGuigan, 1916; Lang, 1931). *The mechanism of the hypoglycemic action* of atropine is not clear. It is not due to paralysis of hepatic glycosecretory nerves, for atropine does not diminish the glycemic response to the splanchnic stimulation (Macleod, 1906). It does suppress epinephrine hyperglycemia in decerebrate rabbits (Forster and Chalmers, 1933), and piqûre hyperglycemia in fasting rabbits, but not if the liver is rich in glycogen (Macleod, 1934). It diminishes other glycosurias materially, but not chloroform glycemia, which is probably asphyxial (E. L. Ross, 1919, 1920). It has been asserted that atropine increases the tolerance for carbohydrates in diabetes, but this needs confirmation (Mosenthal, 1912). It has no effect on insulin hypoglycemia in depancreatized dogs (S. Lang, 1933).

Temperature.—Atropine suppresses perspiration, and thus causes a rise of *temperature* with *moderate doses*, notwithstanding the cutaneous vasodilatation. Animals that do not have sweat glands (dog) do not show this rise. *Larger doses* produce a fall of temperature from lessened heat production, the result of the general depression. The final convulsions may again cause a rise.

Gaseous metabolism is increased by therapeutic doses (1 mg.) in man (Higgins and Means, 1915). In dogs, the intravenous administration of atropine diminished the respiratory metabolism and the CO_2 of the blood. This effect is mutually antagonized by pilocarpine (Klemen, 1918).

Uric Acid.—Atropine prevents the increase of uric acid that normally follows the ingestion of food; presumably by preventing the secretion of the digestive juices (Mendel and Stehle, 1914). It also prevents the cinchophen increase (Abl, 1913).

Hepatic Actions and Coagulability of Blood.—The *secretion of bile* is sometimes slightly diminished by atropine. The lymph flow may be either increased or unchanged (Yanagawa, 1916). The injection of large doses of atropine into the portal vein lowers the *coagulability of blood*, first that of the hepatic vein. This effect is not produced by injection into the jugular vein, or by addition of atropine to shed blood, but is due to an action on the liver. The anticoagulant substance is also produced by the perfusion of atropinized blood through an excised liver (Doyon, 1910).

The **leukocytes** are not changed by ordinary doses. Toxic doses, especially when often repeated, diminish the eosinophils. The action is probably indirect (Herrick, 1914). The emigration of leukocytes in exposed mesentery is not inhibited by atropine or scopolamine (Ikeda, 1916).

Yeast fermentation is stimulated by small quantities, inhibited by large doses (Somoggi, 1916).

Circulation.—*Single therapeutic doses* of atropine do not usually affect the pulse rate materially, but *ordinary experimental doses* greatly increase the heart rate by paralyzing the vagus endings. Atropine *abolishes cardiac inhibition by all drugs* which act through the vagus mechanism, whether they stimulate this reflexly (ammonia or chloroform inhalation); centrally (picrotoxin or veratrum), or peripherally in the ganglia (nicotine), or in the endings (pilocarpine, cholines, muscarine). The blood pressure rises moderately, mainly through the quickened rate, but partly through central vasomotor stimulation. If the blood pressure has been abnormally lowered by excessive vagus stimulation, the atropine rise appears correspondingly greater. The cutaneous vessels are actively dilated. *Toxic doses* paralyze the vasomotor center and eventually also the arterial and cardiac muscle, so that the blood pressure falls profoundly.

Changes of Heart Rate.—Atropine stimulates the vagus center in common with the other medullary centers. It may therefore cause a slight *primary slowing*, which is soon overcome by the peripheral paralysis. This vagus paralysis results in *quickened heart rate* in all animals in which the vagus is tonically active (in man, the cat, dog, etc.). In completely atropinized dogs and cats the rate is about 140 to 240 per minute. The vagus tone being small in rabbits and frogs, these animals show little or no quickening; but in them the vagus is also paralyzed, for its stimulation does not slow the heart.

Electrocardiogram.—In dogs, small doses of atropine usually produce auriculo-ventricular block. With larger doses this is followed by increased sinus rate. At the same time it abolishes any existing blocks, sinus arrhythmias or ectopic beats (as with digitalis). In this last respect, atropine is more efficient than nitrite. The A-V conduction is usually slowed by small and quickened by large doses. The P wave at first tends to negative, then to more positive (Halsey, 1917). In *intact animals*, atropine increases the auricular, but decreases the ventricular, efficiency (Wiggers, 1916).

Therapeutic Use of Vagus Action.—The paralysis of the vagus endings indicates atropine (1 to 2 mg., $\frac{1}{60}$ to $\frac{1}{30}$ grain, hypodermically, repeated as needed) in conditions of excessive vagus stimulation, such as cerebral pressure; the reflex vagus inhibition of colic, of angina, of chloroform anesthesia; operations about the vagus trunks, etc. Atropine also abolishes such cardiac irregularities as are due to heightened vagus excitability (pulsus respiratorius), and it may be used to diagnose whether a cardiac slowing is due to vagus stimulation. In fact, however, response to atropine (or amyl nitrite) merely shows that the heart is still under vagus tone—not that the bradycardia was of vagus origin (Fredericq, 1916). It has been found clinically effective in sino-atrial block (N. W. Brown, 1919; 0.5 to 1 mg.). It has no effect in complete heart block (van Egmond, 1913).

Atropine on Normal Human Heart Rate.—The hypodermic dose of 0.5 mg. produces either no effect or slowing, to about 69, attributable to central vagus stimulation. With 1 mg., this slowing is complicated by a tendency to irregularity. With 2 mg., the slowing is transient, and is followed by quickening. This dosage is the minimum that can be relied upon to depress the vagus (Platz, 1923). The vagus tone is greatest in middle life, between twenty and thirty years, less in old age (after fifty years), and least in infancy; the response of the heart rate to atropine varies accordingly.

Both *sexes* react practically alike, but there are considerable individual variations. These have no constant relation to the rate before the injection (J. H. Crawford, 1923). Paskind, 1921, reports that the slowing by small doses is practically absent in the *Negro race* (twenty cases); but their normal rate averages about ten beats lower than in the white race, so that the vagus center is probably already in a somewhat higher tone and therefore less susceptible to further increase. The later accelerator effects are the same in both races.

Atrio-ventricular rhythm may occur in man from doses of 1 mg. It sets in within eight to ten minutes, soon reaches a maximum, and then disappears. Wilson, 1915, assumes that atropine releases the A-V tissue from vagus control somewhat before it releases the sinus.

Atropine Test for Typhoid Fever; "Vagotonia" and "Sympathicotonia."—In fever, when the vagus control is weak, atropine (2 mg.) does not produce much further quickening. This was suggested as a test for typhoid fever (F. A. Marris, 1916), but it may be absent in this disease and is often present in other fevers, exophthalmic goiter, etc. (J. H. Crawford, 1923). The sensitiveness to pilocarpine and especially to epinephrine is also often altered in typhoid fever (Matsua and Murakami, 1918), but again is not characteristic. Eppinger and Hess, 1909, suggested that the response to these drugs would reveal disturbances in the equilibrium of the sympathetic and parasympathetic innervation; but when disturbances exist, they often involve both systems.

Response in Cardiac Diseases.—In chronic heart disease, in which the sino-auricular node is in control, the response to atropine is diminished; auricular fibrillation shows increased response (J. H. Crawford, 1923). Removal of nodal rhythm by atropine (milligram doses) has been reported (L. F. Bishop, 1921).

Atropine on Voluntary Tachycardia.—N. B. Taylor, 1922, reports a student who could voluntarily increase his heart rate from 70 to 125 along with other manifestations of sympathetic stimulation (glycosuria, vasoconstriction, mydriasis). After 2 mg. of atropine, which raised the heart rate to 90, the rise by volition was only to 115.

Atropine Response in "Effort Syndrome" with Irritable Heart.—The pulse rate responds with the normal incipient slowing, followed by an increase which is generally greater than normal, *i. e.*, six to thirty per minute. The respiratory quotient is slightly lowered. The basal metabolism remains unaffected (Sturgis *et al.*, 1919).

Influence of Heart Rate on the Output of the Heart.—Atropine, 1 mg., hypodermically in man, increases the minute output of the heart in about three-fourths of the subjects, but not as much as the rate (Suarez *et al.*, 1943). When the rate exceeds 80 per minute, it tends to lessen the amplitude of the excursions, for a faster rate does not permit time for the complete diastolic filling of the heart.

Results of Vagus Stimulation after Atropine.—In dogs, when the atropine action has gone just so far that *stimulation* of the *divided vagus trunk* causes no perceptible slowing, this still produces a slight fall of blood pressure; larger doses abolish this response also, so that the inotropic properties of the vagus terminations seem to be somewhat more resistant than the chronotropic. When the *intact vagus* is stimulated in atropinized mammals, the blood pressure may fall or rise by stimulation of the afferent vasodilator or constrictor fibers which run in the vagus. In atropinized *frogs*, the inotropic as well as the chronotropic functions of the vagus are paralyzed (Ransom, 1917). The refractory phase is lengthened (Junkmann, 1925). Stimulation of the vagus trunk quickens the heart, since this carries the accelerator fibers, which are not affected by atropine.

The *dosage* required to paralyze the vagus was studied by Pilcher and Sollmann, 1914. It varies somewhat in different animals, even of the same species, and even for the two vagi of the same animals; the left vagus is more susceptible. Low blood pressure increases the susceptibility. In every respect, the susceptibility to atropine is inverse to the natural excitability of the vagi. In the dog, about 0.01 mg. per kilogram lessens the response to vagus stimulation perceptibly; and about two or four times this dose abolishes the response completely. When the paralysis is incomplete, a slight further slowing may be secured by strengthening the stimulus; but with the larger dosage even the strongest stimulus remains ineffective. *The duration of the paralysis* varies with the dose and with the species. It lasts only a few minutes in rabbits (Rossbach, 1879), longer in goiterous rabbits (Fleischmann, 1911). In dogs and cats, a partial effect persists for hours (Pilcher and Sollmann).

Atropine after Double Vagotomy.—If both vagi of an animal be divided, there is usually no regeneration apparent, even after long periods; nevertheless, the fast rate gradually returns to normal, but atropine at this stage causes marked quickening (F. T. Rogers, 1920).

Perfusion of Turtle's Medulla.—Atropine, 0.02 per cent, has practically no effect on the heart rate or rhythm (Bush, 1919).

Action on Cardiac Muscle.—Atropine has slight direct effects on the *cardiac muscle*, but these are insignificant in the systemic administration. They may be observed in the isolated heart and on the nerve-free heart of the embryonal chick. Small doses stimulate the muscle, causing an increased tonus, greater excursions and some slowing. Turtle heart perfused with 1:25,000 shows only some depression of conductivity (Wedd and Blair, 1945). In the auricles of *terrapin*, atropine is said to increase the tonus, without affecting the periodic tonus waves (Gruber and Markel, 1918). An exhausted frog's heart may be made to beat again. Large doses diminish the tonus and may slow or quicken the rate.

In the *excised mammalian heart* (Langendorff method) atropine provokes rhythmic contractions of the apex after the base is clamped. This requires larger doses than are needed for paralyzing the vagus. These large doses may also restore the beat when it has been arrested by muscular poisons (Luchsinger, 1881).

In the isolated heart of snails, atropine produces slowing with increased amplitude (Boyer and Hazard, 1927).

Cutaneous Circulation and Skin Eruptions.—Atropine produces intense *scarlet or crimson flushing of the skin*, particularly of the face and chest, occurring as extensive erythematous spots, or as a continuous *erythema* which has sometimes been mistaken for scarlatina. This effect is much greater in some patients than in others; it may occur with therapeutic doses. It is due to active dilatation of the cutaneous vessels (vasodilator stimulation), with increased general blood pressure. The hyperemia may be so intense as to lead to desquamation.

The **vasomotor center** is moderately stimulated, but not sufficiently to raise the blood pressure when ordinary doses are injected after dividing the vagi (Sollmann and Pilcher, 1910).

Peripheral Action on Blood Vessels.—Large doses of atropine prevent the dilator effect of cholines (Hunt, 1918). They also antagonize the constrictor action of epinephrine, but not of pituitary (Regniers, 1926).

The coronary arteries are constricted by atropine in dogs (Katz and Lindner, 1939). Atropine has no effect on the normal *pulmonary vessels*, but removes the constriction of pilocarpine or histamine (Berezin, 1914). *Cerebral vessels* are dilated (Berezin, 1916).

Respiration.—Therapeutic doses (1 mg. hypodermically in man) stimulate respiration, increasing somewhat the rate and minute volume, and sometimes the depth of the respiration. The excitability of the respiratory center is not increased directly, for the alveolar CO_2 tension is unchanged. The stimulation is therefore indirect, due partly to increased CO_2 production (increased gaseous metabolism), partly to increased "dead space" in the lungs by bronchial dilation (Higgins and Means, 1915). Toxic doses produce late depression of the center (Binz, 1896), which is the usual cause of death in atropine poisoning.

Therapeutic Uses of Respiratory Stimulation.—The mechanism of this respiratory action in man would render its usefulness doubtful. On the basis of the animal experiments (which, however, involve larger doses) it has been used against poisoning by morphine, and as a preliminary to anesthesia, or even as a restorative in anesthetic fatalities (Webster, 1908). It is also often used in whooping cough, but is of doubtful efficiency (child of one year, 5 mg., $\frac{1}{12}$ grain, of Extr. Belladonna, or 8 to 10 drops of Tr. Bellad. three times daily, doubling the dose in a week if tolerance is acquired; A. Jacobi, 1907).

Respiration in Animal Experiments.—The results have been contradictory. Heinz, 1890, found no appreciable change in the respiratory volume of rabbits; Wood and Cerna, 1892, increased rate and minute volume in dogs. According to most observers atropine *counteracts respiratory depression* from chloral (Husemann, 1877) or morphine (Voegtlin and Wiggers, 1918); but others found that it augments the morphine depression (Orlowski, 1897). Atropine was ineffective against depression of the respiration by cerebral compression (Loevenhart *et al.*, 1918). Hanzlik, 1923, found that 1 mg. (hypodermically) per Kg. of rabbit (without anesthesia) depressed the respiration. With morphinized rabbits, Meissner, 1923, recorded increase of depth without change of rate, from the intravenous injection of 1 to 10 mg. of atropine. With *larger doses*, the psychic excitement and muscular activity increase the respiration indirectly. *Toxic doses* depress respiration, producing slowing, Cheyne-Stokes type, and finally cessation. Artificial respiration may enable an animal to survive six times the fatal dose.

Effects on Psychic Functions.—Therapeutic doses of atropine have no perceptible effects on psychic functions. Overdoses produce symptoms superficially resembling those of alcoholic inebriation. Exaltation and stimulation are more prominent, passing from mere restlessness to hallucinations and delirium, and even mania; and the effects are much more lasting. Similar symptoms can be seen in animals. With toxic doses the stimulation passes into coma, convulsions and asphyxia.

Atropine Alkaloids on the Cerebral Functions of Rats.—Judging by behavior in the circular maze, atropine, scopolamine, homatropine and their derivatives alike produce stimulation in small doses and depression with large doses, but differ materially in the absolute dosage. The action is associated with the tropine and oscine (scopoline) nucleus, and appears to be potentiated by the tropic acid, which is itself inactive. The levo-compounds are more active than the racemic (Macht, 1923). The *convulsions* are not entirely asphyxial, for they are not abolished by artificial respiration. The *vision* is disturbed more than can be explained by loss of accommodation. The *motor areas* in dogs are stated by some observers to be more excitable, but others deny this. *Homatropine* was reported by Issekutz, 1927, as having a fiftieth of the potency of atropine, for central effects. In *frogs*, atropine first increases the reflexes; this is followed by general paralysis and this again by late tetanus.

Atropine and Novatropine in Insulin Hypoglycemia.—J. P. Quigley, 1937, reported that moderate doses of atropine (0.6 to 1.8 mg.) or novatropine (2.5 to 3.5 mg.) counteract promptly the acute symptoms of moderate hypoglycemia induced in normal man by 12 to 20 units of insulin, but about half an hour later many of the subjects developed pronounced mental disturbances, chiefly amnesia, confusion, automatism and speech disturbance, different from the normal effects of either atropine or insulin. They disappeared on administration of carbohydrate.

Atropine against Postencephalitic Parkinson's Syndrome.—Atropine and scopolamine are used against muscle rigidities, especially those following encephalitis (Roemer), often with considerable relief of the muscular stiffness, disturbances of speech and writing, the tics and salivation, improvement of the restlessness and depression, but with little improvement of the psychoses and tremor.

Large doses are usually necessary, beginning with 0.75 mg. and increasing gradually to 15 or even 20 mg. of atropine per day. Scopolamine is more effective against the tremor and rigidity. *Amphetamine* controls the rigidity but not the tremor. *Epinephrine* increases both tremor and rigidity. *All the actions are central,* scopolamine probably depressing the cortex, amphetamine stimulating the basal ganglia (Loman, Myerson and Myerson, 1942). The response to atropine and scopolamine is only symptomatic and the administration must therefore be continued. The side actions are not sufficiently serious to preclude this use and mostly disappear with continued employment. Anorexia, diarrhea and emaciation may persist. Caution should be used in cardiovascular diseases (Marinesco and Facon, 1936). The action is probably on the proprioceptive reflex. Other reflexes are normal in atropinized decerebrate cats (L. Davis and Pollack, 1930).

The "*Bulgarian treatment*" with a white wine extract of Bulgarian belladonna root, introduced by Ivan Raeff, 1926, was claimed to give better results with a smaller equivalent of alkaloids (Fabing and Zeligs, 1941; Price and Merrit, 1941). Similar claims were made for artificial mixtures of hyoscyamine, atropine and scopolamine (Vollmer, 1940). It may be doubted whether this superiority is critically established.

Striped Muscle.—Large doses (greater than could be used in living mammals) block the response to nerve stimulation, similar to curare (Haffner, 1918). Smaller doses (but greater than suffice to paralyze parasympathetic responses) antagonize physostigmine twitchings (E. Frank and Nothmann, 1921), acetylcholine contracture (Riesser and Neuschloss, 1921), nicotine, veratrine, Tiegel and potassium tonus, but not chloroform, caffeine or thiocyanate contracture.

Anodyne Action.—Belladonna liniment or plaster is applied topically for the relief of pain, especially neuralgic and rheumatic. Belladonna suppositories (extract, 0.1 Gm., 1½ grains) are also used in painful hemorrhoids. The rationale is not clear, as atropine is not a local anesthetic.

Dosimetric Tabulation.—The following (adapted from Schmiedeberg) shows the usual progressive effects of therapeutic and toxic doses: 0.5 mg., slowing of pulse and slight dryness of throat; 0.5 to 1 mg., dryness in mouth, often with thirst; 2 mg., pupil dilated, not quite immobile, and increase of pulse rate; 3 to 5 mg., headache, dysphagia, alteration of voice, muscular weakness, restlessness; 7 mg., considerable dilatation of pupils, disturbance of vision; 8 mg., excitement and muscular incoordination more marked; 10 mg., apathy, hallucinations or delirium, unconsciousness.

Atropine Poisoning.—Atropine is readily absorbed, somewhat even from the intact skin, so that toxic symptoms have been observed after the use of belladonna plasters (Doland, 1906). They occur rather commonly in ophthalmic use, through the lacrimal ducts. Where the plants grow wild, the seeds of stramonium ("Jimson weed") and the berries of belladonna are often eaten by children.

Course.—The symptoms set in promptly, but usually run a long course, lasting five to fifteen hours, or even several days in fatal cases. The first to be noticed are those arising from *dryness of the mouth and throat:* difficulty of deglutition and articulation, great thirst, a sense of burning and constriction in the throat. On the eyes, the dilatation of the *pupils,* impaired vision, absence of reaction of light will be noticed. There is often *nausea* and sometimes vomiting. *Excitement,* passing into delirium, is a prominent feature. The delirium may be pleasing, with spectral illusions; or anxious or furious. The onset of the *paralytic symptoms* is ushered in by giddiness, numbness of the limbs and staggering gait, and passes into drowsiness and stupor. The *pulse* is quick (to 170) and small. The respiration is stertorous, fast or slowed. The face is flushed scarlet. In *fatal cases* death is preceded by coldness of the extremities, rapid and intermittent pulse and deep coma. Convulsions are rare. Glycosuria is sometimes seen and may be attributed to the asphyxia. *Postmortem* findings are those of asphyxia. The minority (about 12 per cent) end fatally. Recovery has occurred after 7½ grains (488 mg.) of atropine, although the stomach was not evacuated till one and one-half hours later (Comrol, 1933). The usual *fatal dose* of atropine is probably 0.1 Gm. or more for adults; 0.01 Gm. for children. Therapeutically, children bear proportionately larger doses than adults, and this holds also for young animals.

Recovery starts within two days, the respiration, pulse and pupils returning gradually to normal. Sometimes violent delirious symptoms may last for days, and it has happened that patients have been consigned to the insane asylum on a mistaken diagnosis. Physic "slowness," disturbance of vision and some other symptoms may persist for weeks.

The *treatment of atropine poisoning* is usually effective, and the prolonged course gives time for interference. It comprises the chemical neutralization, prompt removal and meeting the symptoms. The delirium is best treated by the ice cap, the general symptoms by pilocarpine (10 mg., ⅙ grain hypodermically, repeated until the mouth is moist). Morphine (10 mg.) is indicated in the early stages, but not after depression has set in. The latter is combated by medullary stimulants (coffee, etc.). Artificial respiration should be kept up if necessary. The effects on the eye may be abolished by the local application of physostigmine.

Chronic atropine poisoning has been reported, especially from ophthalmic use (Tyrrell, 1906). With continued administration, as against Parkinsonian symptoms, the dosage must be increased progressively, indicating some degree of acquired tolerance. This applies also to the toxic dose, but not to the effects on the vagus or oculomotor (Cloetta, 1911).

Excretion.—The greater part of the atropine disappears rapidly from the blood (Cloetta, 1908). It is excreted mostly unchanged, entirely by the urine, mainly within thirty-six hours (in man, a fourth to a third of the amount administered, within fourteen hours; P. Pulewka, 1932). The application of a drop of the urine to the eye of a cat is a convenient test for poisoning.

Mydriasis occurs with a single drop of 1:150,000 solution, equivalent to 0.000245 mg. of atropine. Of scopolamine, the minimal mydriatic dose is 0.00001855 mg. (Joachimoglu, 1915). The human pupil is about equally sensitive (Metzner, 1912). The antagonism against choline esters on rat duodenum reveals 0.1 gamma of atropine (J. Lévy and Michel, 1938). An adaptation of the chemical Vitali test is sensitive to 10–50 gamma (Morin, 1936). Atropine resists *putrefaction* for a long time and may be found in the cadaver even months after burial. Confusion with putrefactive bases must be guarded against.

The excretion is not complete, more or less of the atropine being destroyed in the body. A part is excreted as tropine and as another base (Fickewirth and Heffter, 1912). Hydrolysis of atropine at the tropic acid: tropine linkage destroys the pharmacologic action (Macht, 1922). The variations in this destruction and in the rapidity of excretion may partly explain the racial and individual idiosyncrasies and acquired tolerance; but the different sensitivity of various animals does not correlate with the ability of their tissues to inactivate atropine; for instance, rats do not inactivate atropine, but are one of the least sensitive species (A. J. Clark, 1912).

Racial and Acquired Tolerance.—Rodents and marsupials are very tolerant, as also, to a less extent, the goat, dog, birds and some other animals. (The dosage for different animals was determined by Wilberg, 1914.) The immunity is not complete. It is perhaps greatest in rabbits, and can be increased by habituation, owing mainly to *destruction of the atropine* by the serum and organs. The atropine appears to be promptly bound by the plasma protein and then gradually hydrolyzed by esterase (Beutner, 1943).

The liver plays a large part in this destruction, and suspensions of liver cells also have this effect (Fleischmann, 1913). The serum of man, dogs and rats generally lacks this quality, which varies considerably in degree in different rabbits. Kako, 1926, claimed that the destruction of atropine by rabbit's blood is decreased after thyroidectomy, and Ikoness and Kusnetzowa, 1927, claimed this for dogs and stated that the activity is restored by reimplantation of thyroid. They also claim that the serum of hyperthyroid patients destroys atropine more actively than normal serum, and the reverse for hypothyroid patients.

The detoxication by rabbit's serum is due chiefly to the rapid destruction of the levoisomer, which is also demonstrable *in vitro* (von Oettingen and Marshall, 1934). However, rabbit's serum also binds other alkaloids, especially pilocarpine, so that they become undialyzable (Beutner, 1923). Homatropine and scopolamine are also destroyed by serum. Frogs, like rabbits, tolerate large doses of atropine, through rapid destruction in the liver (v. Oettingen, 1918). The *hydrolysis of homatropine and atropine* was studied by Bernheim and Bernheim, 1938, in various tissues of different animals. Homatropine and the levoisomers are always hydrolyzed more rapidly. The *esterase* is similar to that which attacks ethyl mandelate. It is inhibited by physostigmine. It is present in the liver of guinea pigs and frogs, and in the blood of about a fourth of the rabbits. It is absent from human blood and from that of all other animals which have been studied (Jeanne Lévy and Michel, 1938; Gliock and Glaubach, 1941).

Atropine Tolerance of Infants.—Infants and young unweaned animals often appear to tolerate relatively large doses of atropine. The mechanism is not clear, but it it not due to destruction of the levo-atropine by serum, as it is with rabbits. The urinary excretion of atropine is high, but it is doubtful whether this is an adequate explanation (J. D. Pilcher, 1934).

Cause of Habituation; Excretion in Animals.—Cloetta, 1911, found that nonhabituated rabbits excrete 15 to 20 per cent of the atropine, the excretion being completed in two or three days. (Fickewirth and Heffter find that the total excretion of all bases is about 50 per cent of the administered quantity.) After immunization, the excretion is completed in one day; and as little or none can be found in the tissues, it appears that the rapidity of destruction and excretion has been increased. The destructive power of the serum, however, is not raised (Fleischmann). Normal cats excrete little of the atropine; but by habituation, the excretion is markedly raised, while the capacity for destruction is not increased. With these, therefore, the tolerance is due mainly to the acquired speed of excretion. Dogs excrete about one-third of the atropine within two days (Wiechowski, 1900). Heckel, 1875, found that rabbits and guinea pigs not only throve for weeks on an exclusive diet of atropine-containing plants (Schroff, 1852), but that this exclusive diet could be continued for several generations. A further degree of immunity was thus acquired, so that the mydriatic effect was smaller and the fatal dose (hypodermically) higher. The flesh of these animals contained relatively little atropine, although the meat of ordinary rabbits poisoned with atropine is toxic to other animals and man (Lewin, 1894).

PREPARATIONS.—***Atropine Sulfate**, U.S.P., is a white, odorless, crystalline powder, freely sol. in water or alc. It is incompatible with alkalis, tannic acid and mercuric salts. Watery solutions of the free alkaloid are hydrolyzed rapidly even at room temperature (P. Hardy, 1922), but atropine sulfate solutions may be boiled for half an hour without decomposition (G. Kühl, 1925). Sterilized solutions in ampuls preserve their full activity at least four weeks (Joachimoglu, 1915). Dose, 0.25 to 1 mg., $\frac{1}{240}$ to $\frac{1}{60}$ grain. Commercial atropine is usually contaminated with varying quantities of hyoscyamine (Liljestrand, 1919). *Atropine Sulfate Tablets*, U.S.P.; usual sizes 0.3, 0.4, 0.5, 0.6 and 1.2 mg. ($\frac{1}{200}$, $\frac{1}{150}$ $\frac{1}{100}$ and $\frac{1}{50}$ grain).—*Atropine* alkaloid, U.S.P., is slightly sol. in water, freely in alc. and in oils.

Belladonna Leaf, U.S.P., the dried leaves and tops of Atropa Belladonna, with not less than 0.3 per cent of alkaloids, is the source of ***Belladonna Extract**, U.S.P., which contains 1.25 per cent of alkaloids (dose, 15 to 30 mg., $\frac{1}{4}$ to $\frac{1}{2}$ grain), and the 10 per cent *Tincture*, U.S.P., representing 0.03 per cent of alkaloids (dose, 0.3 to 1 cc., 5 to 15 minims). There appears little justification for the external use of belladonna in the form of *Belladonna Ointment*, U.S.P., and *Belladonna Plaster*.

Hyoscyamus, U.S.P. (Henbane), the dried leaves and tops of Hyoscyamus niger, contains chiefly hyoscyamine with some atropine and scopolamine. The *Tincture*, U.S.P., represents 10 per cent of the drug, about 0.004 per cent of alkaloids. Dose, 2 cc., 30 minims. The *Extract*, U.S.P., contains about 0.15 per cent of alkaloids. Dose, 0.05 Gm., $\frac{3}{4}$ grain.

Stramonium, U.S.P. (Jimson Weed, Jamestown Weed), the dried leaves and flowering or fruiting parts, with branches, of Datura Stramonium, represents at least 0.25 per cent of alkaloid, chiefly hyoscyamine with some atropine and scopolamine. Against asthma, 10 to 20 grains of the dried leaf, smoked in a pipe; hemorrhoids, fissures and painful ulcers, 10 per cent ointment. *Stramonium Extract*, U.S.P., contains about 1 per cent of alkaloid. Average dose, 20 mg., $\frac{1}{3}$ grain. *Stramonium*

Tincture, U.S.P., contains about 0.025 per cent of alkaloids. Average dose, 0.75 cc., 12 minims. The B.P. Tincture represents 20 per cent of the drug. *Stramonium seeds* are sometimes eaten by children and cause serious poisoning.

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HYOSCYAMINE

This is the levo-isomer of the racemic atropine. Cushny, 1903, compared these two alkaloids and the dextro-isomer. He found that the peripheral actions on the iris, cardiac vagus, and glands are twelve to eighteen times as strong with the l-isomer (ordinary hyoscyamine) than with the d-, and about twice as strong as with atropine. Hyoscyamine has some advantage when the peripheral effects are desired, especially in ophthalmic work. Internally, it has no advantage. All the isomers act practically alike on the central nervous system of mammals. The d- has a greater stimulant effect on the spinal cord of frogs. On the intestine, the isomers act quantitatively alike (Liljestrand, 1919).

◆

AGARIC ACID

Agaric acid and the impure mixture *agaricin* are derived from a fungus of the larch tree. It is a white, odorless and tasteless crystalline powder, but slightly soluble in cold water and alcohol. Agaricin was introduced against the night sweats of phthisis by Young, 1882. The effect appears only after some hours (if at all) and then lasts for about twenty-four hours. It is a local irritant and cannot be given hypodermically. Large doses produce vomiting, diarrhea and death through central paralysis (Hofmeister, 1888). It is advisable to start the dosage with 0.5 mg. and increase as needed, but not to exceed 30 mg. per single dose or 100 mg. per day. Clinical opinions differ as to its value. The mechanism of its action has not been satisfactorily explained. Hofmeister claimed that it prevents the sweating response of the cat's paw to sciatic stimulation or heat, indicating that its action is peripheral. It does not arrest the saliva or tears. McCartney, 1917, finds that it has a digitalis action and that it stimulates smooth muscle. Bergstrom, 1928, reports that low concentrations increase the excitability of excised intestines and of the vagus endings of frog heart, that larger doses depress parasympathetic endings and that still larger doses depress smooth muscle directly.

◆

SCOPOLAMINE (HYOSCINE)

The U.S.P. specifies the levorotatory scopolamine. Commercial samples were often rather impure mixtures of two isomeric alkaloids (tropeic esters of oscine or scopine; Willstätter and Berner, 1923, a base closely related to tropine): scopolamine proper (levorotatory) and atroscine (optically inactive). They occur in the various atropine-containing plants, but are now prepared mainly from scopola. The *peripheral actions* of scopolamine agree qualitatively with those of atropine, but there are quantitative differences; for instance, the actions on the oculomotor and secretions are stronger, while the vagus action is relatively weak. The *central actions* differ more profoundly, scopolamine being mainly sedative in all doses, while moderate doses of atropine are excitant. There are great individual variations, however, in the response to scopolamine, and in its toxicity, even with the purest samples, although the uncertain composition of the commercial samples probably played a part.

It was formerly stated that there are specific differences in the effects according to the origin of the alkaloids, and that "hyoscine" derived from hyoscyamus is therapeutically superior to the "scopolamine" of scopola. No such difference exists if the alkaloids are pure; for these are identical, whatever their source (E. Schmidt, 1894).

Apoatropine (also called belladonnine or atropamine) was demonstrated in a commercial sample by Kobert, 1905, and has been held responsible for the occasional toxic effects, but this is improbable. It is a rare impurity (Kionka, 1908), and its presence is easily shown, by reduction (brown color), on adding a few drops of permanganate solution (Kessel, 1906). It exists preformed in the plants and may be derived chemically from atropine by the abstraction of one molecule of water. In rabbits it produces rise of blood pressure, paralysis of cardiac vagus endings, convulsions by central excitation and death with relatively small doses by paralysis of respiration. The oculomotor and secretory endings are not paralyzed. It is more potent than atropine on the intestines, acting directly on the muscle and not on the parasympathetic endings. It is more active by mouth than hypodermically, being destroyed by tissue enzymes as well as by the plasma (Kreitmair and Wolfes, 1938).

Deterioration of scopolamine solutions has been suggested as a cause for toxic reactions, but according to the seemingly more reliable experiments of Kionka, 1908, Willstätter and Hug, 1912, and Beck, 1914, the solutions keep unchanged indefinitely, at least in sealed ampuls. H. Bolten, 1917, described abnormal effects in six patients from a solution that had been kept for several months in a "sterile" bottle (not ampul).

Rabbits' serum destroys the levo-isomer more rapidly than the dextro-, while the rate of destruction is equal in egg white. This holds true also for the hyoscyamine isomers and is therefore due to the tropic acid radical (von Oettingen and Marshall, 1933).

Pharmacologic differences between scopolamine and atroscine are important in the peripheral actions, but not in the more important central effects. Cushny and Peebles, 1905, found that the levo- and rotatory-alkaloids act alike on the central nervous system in mammals, and on the motor endings; but that the levo-alkaloid (scopolamine) is twice as active on the salivary and vagus endings as is the racemic atroscine. This has been confirmed, also for the pupil, by Hug, 1912. Smith, 1915, found the fatal dose the same for mice. Cushny, 1921, states that eleven hyoscine isomers are possible, since both tropeinic acid and oscine are asymmetric. He quotes instances showing that the optical rotation may be involved in some of the actions, and not in others of the same substance.

Psychic Actions.—In man, doses of 1 to 3 mg. ($\frac{1}{60}$ to $\frac{1}{20}$ grain) generally produce, within ten or fifteen minutes, fatigue, drowsiness and a natural dreamless sleep, lasting several hours. The response, however, is variable. In some the sleep is preceded by hallucinations, which may be rather pleasant with small doses, but become violent if the dosage is increased. Animals are also affected differently by scopolamine (Kochmann, 1913).

Dogs react similarly to man: small doses produce sleep and hallucinations; larger doses cause more marked hallucinations and restlessness, ataxia and often emesis. The excitability of the motor areas is said to be lowered (Sohrt, 1886; Ramm, 1893). With white *rats* Barlow, 1932, found small doses (to 13 mg. per Kg.) slightly sedative and analgetic, but never hypnotic. Between 65 and 130 mg. per Kg., it was purely excitant. *Rabbits* react by a mixture of depression and stimulation (Liljestrand *et al.*, 1919). *Frogs* show central abolition of reflexes (Wood, 1883), preceded by more extensive spreading of the reflexes (Kochmann).

Site of the Narcotic Action.—Scopolamine is more potent in rabbits after removal of the cerebral hemispheres, so that it acts apparently, at least partly, on the sleep centers of the midbrain (Mehes, 1929).

Therapeutic Use of Sedative and Hypnotic Action.—Scopolamine is employed especially in acute maniacal excitement, delirium tremens and tetanus. It has *advantages* over morphine, in that it quiets the reflexes and avoids addiction; and over chloral, in that it does not usually depress the medulla. However, it produces the unpleasant *side effects* of mydriasis, cycloplegia and excessive dryness; sometimes muscular tremors and occasionally serious delirium (the latter is said to be promptly controlled by small doses of morphine). The therapeutic dose lies much below the ordinary fatal dose; but small doses (0.2 to 0.75 mg., $\frac{1}{300}$ to $\frac{1}{75}$ grain) have produced serious poisoning, with cardiac and respiratory collapse. On the other hand, $\frac{1}{10}$ and even $\frac{3}{4}$ grain (6.5 and 50 mg.) have been taken without ill effects. Insane patients generally seem to be tolerant, so that the effective doses (1 to 3 mg., $\frac{1}{60}$ to $\frac{1}{20}$ grain) may be given; with ordinary individuals it is not safe to exceed 0.5 mg. ($\frac{1}{120}$ grain), repeating this smaller dose every six to eight hours, if necessary; and it would be safer to use this dosage also for the insane. Smaller doses (0.2 mg., $\frac{1}{300}$ grain) may be used to enhance the hypnotic effect of morphine. The use in *drug addictions* has been discussed under "Morphine."

Prevention of Motion Sickness.—Scopolamine hydrobromide, 0.6 mg. by mouth half an hour or an hour before the trip, protects the majority of susceptible persons against *seasickness* and *airflight sickness* with negligible side effects. It may safely be repeated in eight hours, but beyond this only under medical supervision.

In well controlled trials on experimental sea trips, H. E. Holling, 1944, found the following ratios of susceptible individuals protected: Scopolamine, 0.6 mg., 50 to 75 per cent (the percentage was no better with 1.2 mg.); atropine, 1 mg., 40 per cent; homatropine, 2 mg., 25 per cent. No protection was obtained with barbiturates, with diphenyl hydantoin sodium, 0.2 Gm., and with methedrin, 8 mg. The only *side effect* of scopolamine was dryness of the mouth. There was no drowsiness, no eye symptoms, no impairment of physical performance, but little effect on adjustment to heat. Similar successful trials of scopolamine against *airsickness* are reported by J. L. Lilienthal, 1945. The U. S. Army experimented with a mixture of scopolamine hydrobromide, 0.2 mg., atropine sulfate, 0.15 mg., sodium amytal, 60 mg. Serious and fatal barbiturate poisoning occurred from unauthorized overdosage (Foucar *et al.*, 1946).

"Swing sickness," which appears analogous to seasickness, is prevented in about half the susceptible individuals by the following: scopolamine hydrobromide, 0.5 or 0.75 mg.; atropine sulfate or l-hyoscyamine hydrobromide, 1 mg. Homatropine is less effective; demerol and pavatrine are of doubtful value; barbiturate, amphetamine, thiamine and pyridoxine appear ineffective. Amytal does not add materially to the potency of atropine or scopolamine. Neostigmine decreases the effectiveness of scopolamine, but does not abolish it (P. K. Smith, 1946).

Parkinson's Disease.—Rather large doses of scopolamine (0.8 mg., $\frac{1}{75}$ grain, four to five times per day) often produce some improvement in the tremor and rigidity, and are rather more effective than atropine or hyoscyamine. The action, as with these, is probably central.

Respiration and Circulation.—Therapeutic doses ordinarily do not cause any important effects (Kochmann, 1903). The respiration is practically unchanged. The pulse may be unchanged or considerably slowed (central vagus stimulation). The blood pressure shows no change, or with somewhat larger doses a moderate rise (stimulation of vasomotor center). Toxic doses depress the respiration, the heart and the blood pressure. With fatal doses, the respiration stops before the heart.

The Eye.—The effects of scopolamine correspond qualitatively with those of atropine. They are produced more quickly and by doses only one-fifth or one-tenth as large (Joachimoglu, 1915), but are not quite as lasting. The intra-ocular pressure is less affected (Bollet and Curtil, 1911). It is less irritant than atropine, and patients who do not tolerate atropine can often take scopolamine. It is used like atropine (iritis, etc., 0.1 per cent; cycloplegia, 0.2 per cent).

The secretion of saliva, sweat, mucus, etc., is paralyzed by therapeutic doses of scopolamine, more actively than by atropine.

The effects on the intestine correspond to those of atropine. The *excised uterus* is stimulated (Kehrer, 1907; Barbour and Copenhaver, 1915). *Isomers on Excised Ureters.*—The levo- stimulates the contractions and slightly raises the tone. Very large doses depress. The dextro- inhibits without stimulation. The racemic is also inhibitory (Macht, 1918). *Potassium tonus* is antagonized by scopolamine in the isolated intestine, not in striped muscle (Blumenfeldt and Köhler, 1928).

Scopolamine-Morphine Synergism.—The two alkaloids produce additive narcosis. It is questionable whether there is actual potentiation (Madelung, 1900; Buergi, 1910; Kochmann, 1913; Mehes, 1929) or simple summation of the effects (M. I. Smith, 1915; Storm van Leeuwen and van der Made, 1919). The improvement probably consists in diminution of side effects, such as the deliriant tendency of scopolamine, rather than in intensification of the narcotic action. (*Bromide* also renders scopolamine more hypnotic for rabbits and cats; Mehes, 1929.)

Buergi claimed that a dosage of scopolamine which has no effect when given alone to rabbits (0.1 to 1 mg. per Kg., by mouth or hypodermically) produces narcosis when used with two-thirds of the dose of morphine required to produce narcosis when given alone. Similar "potentiation" was described for a mixture of $\frac{1}{80}$ of the minimal effective dose of morphine with $\frac{1}{2}$ of the minimal effective dose of urethane, or $\frac{2}{5}$ morphine with $\frac{1}{25}$ urethane. Electroencephalograms, which show little change with 1 mg. of scopolamine clinically, react with typical sedation when 10 to 20 mg. of morphine are added (H. Berger, 1934).

Preanesthetic Sedation.—Scopolamine hydrobromide, 0.6 mg., $\frac{1}{100}$ grain, may be injected with morphine sulfate, 15 mg., $\frac{1}{4}$ grain, partly to intensify the sedative action, and partly to diminish mucus and postoperative nausea and emesis similarly to atropine (Waters *et al.*, 1938). Many anesthetists advise against this, as its variable action makes the course of anesthesia more uncertain and therefore more risky. It also tends to add to the respiratory depression of morphine and may cause marked fall of blood pressure (A. Mayor, 1908). It is especially dangerous with chloroform (W. Straub, 1913).

Scopolamine alone is not narcotic (for rabbits or mice), even in large doses; nor does it diminish the concentration of ether or chloroform required for light anesthesia; but it does permit a deep anesthesia with relatively lower concentrations. It also deepens the morphine narcosis. The two alkaloids used together produce a deeper anesthesia with a given concentration of inhalation anesthetic (Ludewig, 1913). With rats, Barlow, 1932, obtained intensification of nitrous oxide-oxygen anesthesia by scopolamine alone. It decreased the effectiveness of morphine premedication and intensified the respiratory depression.

Scopolamine-Morphine Anesthesia.—The combination of adequate doses of the two alkaloids results in a deep narcosis that may permit of major surgical operations (Scheiderlin, 1900). The advantages of exclusive scopolamine-morphine anesthesia, as compared with ether or gas, are rather minor, while the disadvantages are serious (Hatcher, J.A.M.A., 1910, *54:* 446). The combination increases not only the narcotic action, but also the depression of respiration and circulation, and this in irregular degree. The susceptibility varies so much that the surgical anesthesia is often incomplete and must be supplemented by ether; and on the other hand, serious accidents and fatalities are alarmingly frequent. The anesthesia cannot be modified to suit the needs of the moment. Delirium, sometimes serious, is not uncommon. In obstetrics, deep scopolamine-morphine anesthesia is especially dangerous to the child, owing to the great susceptibility to morphine. In nonfatal cases, the child may show somnolence and deficient respiration for days after delivery (Jung, 1914).

Scopolamine-Morphine Amnesia, "Twilight Sleep."—Moderate doses of morphine with rather heavy doses of scopolamine produce narcotic amnesia, a drowsy condition in which consciousness is blunted but not abolished, so that the patient can follow orders. Pain also is felt but blunted. The narcotic stupor lasts from six to ten hours; and when the patient fully wakens, there is no memory of the intervening events and experiences, in successful cases. This seminarcosis, introduced by Gauss, 1906 and 1907, as "*Dämmerschlaf,*" is used in obstetrics "to deprive labor of its terrors." It requires careful management, but those who have experience and skill in its use obtain good results in most cases. Under favorable conditions it probably reduces the maternal and fetal mortality, and diminishes perineal injury, especially for primiparae. It does not interfere with uterine contractions, but if the narcosis is deep it may abolish the abdominal contractions and thus delay delivery. The chief drawback is the variability of the response; it fails not infrequently, and some patients become delirious or maniacal. Toxemia and cardiac dilatation require special caution. Morphine must not be administered within three hours of the end of the second stage, for it delays the breathing of the child.

Doses for Twilight Sleep.—The minutely defined technic involves exclusion of noise, light and all excitant factors—apparently the cooperation of suggestion is essential. The drugs are not started until regular pains occur, perhaps every four to five minutes and lasting half a minute. The first injection is of 8 to 15 mg. of morphine and 0.45 mg. of scopolamine hydrobromide. The morphine must not be repeated. The scopolamine, however, is repeated; first in three-quarters of an hour with 0.45 mg., then every one and one-half hours with 0.3 mg., until amnesia (loss of memory) is sufficiently advanced. This is tested every half hour.

Effects on Uterus.—Morphine and scopolamine amnesia has no constant or marked effect on the uterine contractions clinically (Dodek, 1932), or on anesthetized animals (Barbour, 1915) The alkaloids slightly increase the tone of the excised uterus, without synergism or antagonism (Barbour and Copenhaver, 1915).

Scopolamine during parturition also appears to add amnesic potency to intravenous pentobarbital injection (P. P. Volpitto, 1946).

The toxic effects of scopolamine are similar to those of atropine: dry mouth (xerostomia), vertigo and ataxia, marked mydriasis and disturbed accommodation; mental confusion, loss of memory, muttering, somnolence, deep sleep, stupor, coma; or, exceptionally, delirium and maniacal excitement (McCowan *et al.*, 1926). There is often a Babinsky reflex. The symptoms differ from those of atropine generally by the greater hebetude and by the absence of the scarlatinal rash and pulse acceleration, and usually of the restlessness. The *treatment* consists in alkaloidal antidotes. Central stimulation by ephedrine has been shown to be of some value in cats (Kreitmair, 1926).

***Scopolamine Hydrobromide,** U.S.P. (*Hyoscine Hydrobromide*, B.P.), is the levorotatory isomer obtained from various Solanaceous plants. It occurs as colorless crystals, freely sol. in water (1:1.5) and alc. Dose, 0.3 to 0.6 mg., $\frac{1}{200}$ to $\frac{1}{100}$ grain.

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PILOCARPINE

Pilocarpine, the principal alkaloid of jaborandi leaves (Pilocarpus), stimulates the parasympathetic receptor mechanism, increases secretions, augments the gastro-intestinal movements, constricts the pupils, etc. It also increases the response of all autonomic ganglia to natural or test stimuli (Bacq and Simonart, 1938; Marrazzi, 1939) and thereby increases the output of epinephrine and quickens the heart rate in mammals. It has no effect on striated muscle. The central effects of pilocarpine are unimportant. The peripheral effects are easily inhibited by atropine. Conversely, pilocarpine removes the depressant effects of small doses of atropine, but is ineffective against large doses. Pilocarpine is used as miotic and as diaphoretic; in the latter respect it surpasses all other drugs. Pulmonary disease enjoins caution in its use, since the increase of mucus and the action on the circulation may result in dangerous *pulmonary edema.*

Other Jaborandi Alkaloids.—Pilocarpus contains two other alkaloids, isopilocarpine and pilocarpidine. These differ chiefly in the strength of their action, pilocarpine being the strongest and pilocarpidine the weakest. It was formerly believed that pilocarpus contains another alkaloid, jaborine, with atropine actions. This view was shown to be erroneous (Marshall, 1904).

Arecoline, the alkaloid of Areca or Betel nut, is closely related to pilocarpine in its actions (Marmé, 1889; Leepin, 1891). It stimulates peristalsis (Paetz, 1910) and produces marked bronchial constriction by peripheral action, but is overcome by atropine or epinephrine (D. E. Jackson, 1914).

Glands.—Pilocarpine increases the secretion of saliva, sweat, tears, mucus, of the gastric, pancreatic and possibly of the intestinal juice and of the milk, not of the urine or bile. A gallon of water may be removed by these secretions, after a single injection.

Microscopic Changes during Pancreatic Secretion.—As described by E. Ries, 1935 (from fixed preparations), the proenzyme granules of the pancreatic cells are formed from "lipochondria," which contain fat and take basic vital stains. After pilocarpine, or feeding, these proenzyme granules are discharged, and the lipochondria form daughter granules, which increase, are transformed into proenzyme granules and discharged. The nucleus of the cell does not undergo any changes in the process.

Smooth muscle is contracted practically everywhere, in the eye, bronchi, uterus, ureter, bladder, spleen, stomach and especially in the intestines, resulting in diarrhea and colic. The blood vessels are not contracted.

Paradoxical Effects.—In several situations, and under special conditions, the effects of pilocarpine correspond to stimulation of the sympathetic. This has been attributed to increased output of epinephrine, but acceleration occurs also in the excised heart and excised intestine.

Suprarenal Stimulation.—Dale and Laidlaw, 1912, describe evidences of oculomotor stimulation even if the cervical ganglia have been excised, but not if the suprarenal has been removed. They ascribe this to stimulation of the suprarenals, *i. e.*, increased production of epinephrine. There is a similar condition as regards the uterus. Jackson, 1913, accepts the same explanation for a dilator effect on bronchial muscle. However, Stewart and Rogoff, 1916, showed that pilocarpine does not increase the output of epinephrine.

Direct application of pilocarpine to the hypothalamic centers (by injection into the lateral ventricles of human patients) produces effects analogous to those of intravenous injection: quickened pulse, sensation of heat, abundant salivation, emesis (Cushing, 1931). In rabbits it also causes mydriasis, exophthalmos, hyperthermia and gastric ulcers (R. Light *et al.*, 1932). Apparently pilocarpine acts locally on the parasympathetic centers of this region.

Eye Effects.—Topical application of pilocarpine produces miosis and spasm of accommodation, by peripheral stimulation of the oculomotor.

In rats and guinea pigs, pilocarpine dilates the pupil (J. A. Waddell, 1926; Koppanyi). The miosis begins in fifteen minutes (independently of the concentration), reaches its maximum in thirty to fifty minutes and disappears in twenty to twenty-four hours. The spasm of accommodation also begins in fifteen minutes, and lasts about two and a half hours. The intra-ocular tension is first raised, followed by more persistent fall. Pilocarpine nitrate in $\frac{1}{4}$ to 4 per cent solution is applied as a milder substitute for physostigmine in glaucoma, corneal ulcer, etc.

Diaphoretic Action.—To produce this effect, pilocarpine should be injected hypodermically (5 mg., $\frac{1}{12}$ grain), the patient being kept warm. This dose may be repeated in half an hour if necessary. Several liters of sweat may be excreted. The diaphoretic action is used in *nephritis,* to relieve the kidneys and to remove edema. This dosage usually produces salivation, sweating and nausea, often vomiting and singultus; exceptionally, slowing of the pulse; sometimes considerable general depression, and with larger doses serious collapse, especially in children.

Pilocarpine causes sweating after degeneration of the nerves, though less than on the sound side (Langley and Anderson, 1904). It is completely antagonized by atropine and diminished by epinephrine—the latter perhaps through vasocontriction. In paralyses of the cortical psychomotor region, the corresponding parts of the skin are reported to perspire especially strongly in response to pilocarpine (Bikeles and Gerstmann, 1915). *Acceleration of the blood current* through the glands occurs as a secondary effect of their increased action. A common effect of pilocarpine, a *hyperemia of the skin* (resulting in an increase of its temperature), may possibly be due to the greater activity of the sweat glands. The increased circulation of the skin is said to augment the *growth of hair* and to darken its color. The statement may be doubted.

Other Diaphoretics (Sudorifics or Hidrotics).—The secretion of sweat may be increased (1) by stimulating the secretory structures, (*a*) peripherally (pilocarpine, furmethide, acetylcholine) or (*b*) the sweating center (camphor, ammonium acetate); or (2) by increasing the cutaneous circulation, (*a*) locally (mustard; external heat) or (*b*) through the vasomotor center (internal heat; alcohol, salicylates, acetanilide, nauseants etc.): Children sweat more, old people less easily, than adults. Among animals, horses sweat most profusely; pigs and beef, not readily; dogs, rabbits and sheep, not at all; cats only on the paws.

Indications for Diaphoretics.—The sudorific measures specially adapted to the different indications are as follows:

For the Absorption of Edemas and Exudates.—A powerful action is needed: pilocarpine combined with external heat (hot baths or packs).

To Relieve Inflamed and Overtaxed Kidneys.—The large amount of fluid and excrementitious material removed by a thorough sweating secures functional rest to the kidneys and lowers blood pressure. Here, also, pilocarpine and hot baths are preferred.

Ordinary sweat (Hoelscher, 1904) contains 0.22 to 0.81 per cent of ash, and 0.043 to 0.084 per cent of *nitrogen,* mainly in the form of urea (0.285 per cent of NaCl and 0.21 per cent of urea; Kovesi). The daily cutaneous excretion of nitrogen is from 0.3 to 1.8 Gm. (Benedict, 1905; Schwenkenbacher and Spitta, 1907). Even during rest, the sweat averages 0.07 Gm. of nitrogen per day. This is considerably increased, in proportion to muscular labor, to 0.22 Gm. of nitrogen per hour (F. C. Benedict, 1905). The proportions of *Cl, Na and K* in human sweat vary considerably for different individuals. The *lactic acid* concentration is much higher than in the blood. The reaction is ordinarily acid to *p*H 4.4 (A. G. R. Whitehouse, 1935). The *p*H of pilocarpine sweat ranges from below 5.4 to 7.6, being less acid than that from light-baths (4.5 to 6.5; A. Marchionini, 1929). The acidity of sweat appears to be due to substances given off by the epidermis; normal sweat from the glands has the slight alkalinity of blood plasma (Whitehouse).

The sweat excreted under the influence of pilocarpine contains in normal individuals 0.051 to 0.085 per cent of nitrogen, and 0.26 to 0.31 per cent of ash. Three liters of sweat—a not unusual quantity after pilocarpine—would therefore remove about 2.5 Gm. of nitrogen. In nephritis, the nitrogen content may be much higher, to 0.288 per cent, so that the 3 liters could remove 8 Gm. of nitrogen. The abnormally great depression of the freezing point of the blood of uremic patients may be reduced to normal by diaphoresis (Bendix, 1904). The freezing point of the blood of normal animals is not affected. Alimentary glycosuria could also be prevented by free diaphoresis, the excess of sugar being excreted by the skin. However, Austin and Miller, 1914, could find no evidence that sweat baths materially diminish the nitrogen retention in nephritis.

For the removal of poisons, especially in chronic intoxication by the metals, the efficiency is doubtful. Hot baths and drinks would be used.

To reestablish disturbed circulation in the skin, and thereby to influence the circulation of internal organs, determines their use in colds, rheumatism, etc.; in cold skin from whatever cause; in inflammations of the lungs, pleura, etc. Relatively mild diaphoretics suffice for this purpose: external heat; hot drinks (tea, lemonade or alcohol); Sweet Spirits of Nitre; Dover's powder; salicylate, etc.

The increased vascularity of the skin is used to hasten the outbreak of *febrile exanthemata, to promote the absorption of salves, etc.*, and in certain *diseases of the skin* where its nutrition is defective. In *ophthalmology*, diaphoresis has been reported useful in congestive and exudative lesions of the uveal tract, in retinal detachment and in toxic blindness; it is useless in atrophic and cicatricial lesions.

Pilocarpine Salivation.—The *sialagogue* action is employed (10 mg., $\frac{1}{6}$ grain, by mouth, three or four times a day) against poisons which suppress this secretion (atropine, meat poisons, etc.). The increased secretion of *mucus* may be used in a dry cough. This also results in loosening croupous membranes. The increase in biliary mucus is said to facilitate the passage of *gallstones*. Its utility is doubtful.

In man, 5 to 10 mg. of pilocarpine, by mouth, increase the volume of saliva considerably. The percentage of inorganic solids is unchanged; that of organic solids shows an insignificant increase. The proportion of ptyalin is markedly diminished, but its total quantity is considerably increased (Ewing, 1911). In dogs, hypodermic injection of 0.5 mg. per Kg. raises the chloride concentration of the saliva and lowers it in the blood, increases the metabolism of the salivary glands and decreases the sedimentation rate of the erythrocytes (Vladesco and Nichita, 1939). The composition of pilocarpine saliva is not changed by the injection of sodium phosphates, sulfate or carbonate, or of glucose, unless toxic doses are given (Asher, 1908). The submaxillary gland, when *perfused* with Locke's solution, can be provoked to secretion by pilocarpine, but not by chorda stimulation (Demoor, 1912).

Gastric Secretion.—Pilocarpine increases the volume and the enzymes of the gastric juice (Chiari, 1913), clinically as well as in animals, even when histamine is ineffective (Blakely and Wilkinson, 1933). Mucin is increased but little, if at all (F. Hollander, 1944). Reports as to acidity are contradictory. The effects have a relatively long latent period and long duration (Hollander and Stein, 1943).

It is usually stated that the *acidity* is markedly decreased even to total anacidity (Blakely and Wilkinson, 1933). It is more potent if injected into the lateral ventricles. It is antagonized by atropine, but only with difficulty by histamine (Ferguson and Smith, 1934). On the other hand, Hollander, 1944, claims increased secretion of gastric acid.

Gastric Motility.—Pilocarpine quickens the peristalsis of the prepylorus and increases the tonus of the pylorus (Schroeder, 1933). The stomach generally begins to empty earlier, but its complete evacuation is delayed (Herrin, 1936). The effects are antagonized by atropine.

Acute hemorrhagic erosions of the gastric and duodenal mucosa occur in rabbits after repeated doses of pilocarpine (five injections of 25 mg. at intervals of twenty-five minutes), also after histamine (five injections of 7.5 mg.). They have not been observed after physostigmine and choline. They differ from clinical gastric and duodenal ulcers in that they do not become chronic. They are probably due to mechanical injury of the thin gastric wall of rabbits by the violent muscular contractions induced by the drugs, especially when it is filled with coarse food. They are not easily produced in the cat and rat and are somewhat different in guinea pigs (Underhill and Freiheit, 1928).

The pilocarpine nausea and emesis arise reflexly from the parasympathetic disturbance, especially of the heart, and presumably also the gastric movements. They are antagonized by atropine and do not occur on direct application of atropine to the medullary vomiting center (Kwit and Hatcher, 1933).

Pancreatic Secretion.—Lannoy, 1905, claimed that this is not increased if the pylorus is ligated. He therefore believed that the ordinary increase is indirect, due to the increased secretion of acid in the stomach, and therefore increased production of secretin. However, Camas and Gley, 1913, find that it is effective even when the small intestine has been removed, so that it must act directly on the pancreas.

Succus Entericus.—Kubikowski, 1927, reported that this is increased, the fluid more than the enzymes, by pilocarpine, physostigmine and choline.

Milk Secretion.—Earlier investigators claimed some increase (Roehrig; Ott and Scott, 1912), but Hays and Thomas, 1920, found the response inconstant and within the range of accidental variation. Other reputed lactagogues were also ineffective.

Bile and Lymph Flow.—Janagaw, 1916, claims that these are increased.

Cerebrospinal fluid is increased by the respiratory embarrassment (Dixon and Halliburton, 1913).

Oviduct Secretions.—Pilocarpine has practically no effect on the albumen or shell production in birds (Riddle and Wing, 1921).

Development of Ova.—Sollmann, 1904, described the phenomena of antagonism to atropine.

Yeast Fermentation.—Somogyi, 1916, claimed that this is inhibited by small concentrations, but stimulated by larger doses.

Intestinal motility is stimulated by pilocarpine, in man and most animals. Moderate doses speed the propulsion, but the effects are erratic and not very marked (soft bolus, permanent loop of jejunum, dog; Quigley *et al.*, 1934). Large doses cause violent peristalsis and colic.

Paradoxical Relaxation.—Excised intestine of *frogs* is generally relaxed by pilocarpine. This antagonizes barium contraction and is additive with atropine relaxation (G. B. Roth). With excised intestines of *rabbits*, pilocarpine and arecoline contract if applied separately, but relax if used together (Busquet, 1933).

Other Smooth Muscle.—Pilocarpine generally stimulates the *bronchioles*, *uterus* and *urinary bladder*, as discussed under Autonomic Actions (see Index). It stimulates the gallbladder (Lieb and McWhorter, 1915).

Contraction of the spleen (Palitz and Morse, 1936) results in increase of blood cells (Bornstein and Vogel, 1921) and leukocytes, the latter being aided by the contraction of the smooth muscle of the lymph glands (Harvey, 1906).

Circulation.—The effect of clinical doses is not important. With doses of 7.5 to 10 mg., Blomberg and Ronnel, 1930, report pulse acceleration of 13 to 17 per minute, and 4 to 7 mm. rise of blood pressure. Intense nausea and vomiting may modify these effects. The *cardiac acceleration* is contrary to what would be expected from parasympathetic stimulation, but it is the usual result with mammals (not with frogs). It has been attributed to increased epinephrine output, but it occurs also in the excised heart.

Excised Mammalian Heart (Hedbom-Langendorff).—The effects are similar to those in the frog heart, but the stage of vagus stimulation is short: the rate is suddenly slowed; this lasts a short time, then there is marked quickening with increased tonus. If the auriculoventricular bundle is divided, pilocarpine or muscarine does not produce inhibition (Cullis and Tribe, 1913); nor do they inhibit isolated ventricular strips (Leetham, 1913). Their action must therefore be on the auricular vagus terminations. Large doses paralyze the muscle. The *frog heart* responds with vagus stimulation; *i. e.*, slowing and weakening, and diastolic standstill (Harnack and H. Meyer, 1880). The slowed rate decreases the oxygen consumption (David, 1930). Atropine prevents both the chronotropic and inotropic effects; both are also antagonized by epinephrine and by caffeine; digitaloids antagonize the weakenings, but not the slowing (F. Ransom, 1917). The slowing occurs after nicotine (Galsboeck, 1911) and is therefore probably postganglionic. The vagus excitability is increased. Combinations with muscarine give additive effects; physostigmine does not (Loewi, 1912). The sympathetic innervation is not affected (Barlow, 1936). High concentrations paralyze the cardiac muscle. Small doses of chloral, by depressing the cardiac muscle, delay the escape from *vagus* inhibition, whether by pilocarpine, muscarine or electric stimulation (Loewi, 1912). Pilocarpine arrests the contractions of *terrapin's heart*, but does not affect the auricular tonus waves (Gruber, 1920).

The blood pressure of dogs falls by vasodilatation, after intravenous injection of 0.1 mg. per Kg. With larger doses this is followed by considerable rise, which is increased by nicotine, decreased by cocaine, and abolished by atropine and by pentobarbital (Koppanyi, 1939). Nelson and Keiper, 1923, observed that with small doses, the organ volume may increase after the fall of blood pressure. *Perfused blood vessels* are dilated (frogs; Froelich and Pick, 1913). Berezin, 1914, claims constriction of the lung vessels.

Pilocarpine (1:1000) has a true *curarizing action* in frogs, but not in cats. The nerve-muscle block is not antagonized by atropine (G. Coppée, 1943).

The urine output is ordinarily not affected directly (MacCallum, 1905); but the great loss of fluid by other channels usually diminishes the water and chloride output by the kidneys (Asher, 1905; Cow, 1912). Repeated injections of large doses produce glycosuria and diuresis, which Waterman, 1911, attributes to increased renal permeability.

Metabolism.—Pilocarpine somewhat increases CO_2 production and tends to raise the temperature, even in curarized animals, by stimulation of the glands and unstriped muscle. The increase is antagonized by atropine (Keleman, 1918). Mendel and Stehle, 1915, claim that pilocarpine and other stimulants of digestive glands increase the excretion of uric acid.

Blood Sugar Level.—Rather large doses of pilocarpine cause moderate hyperglycemia in normal animals (Hrubetz, 1937). Doses which are not effective alone increase the hyperglycemic response to epinephrine (Belak and Klamartsik, 1930). The hyperglycemia is antagonized by both insulin and atropine (Framaviglia, 1930). It is more marked after excision of the pancreas (Appelrot, 1935). It is attributed to discharge of epinephrine, for it does not occur after excision of the adrenal glands; indeed, pilocarpine then lowers the blood sugar level (Viale and Napoleoni, 1928).

Central Nervous System.—Except for direct injection into the lateral ventricles, the central actions of pilocarpine are weak and appear late, so that they are overshadowed by the peripheral actions. The effects are mainly *depressing*. *Vasomotor paralysis* is a rather early and prominent symptom; it leads to *dyspnea*. Later, the *respiratory center* is also depressed. The *motor centers*, especially those of the cord, show some stimulation (increased reflexes, tremors, convulsions) and later paralysis.

Fate and Excretion.—A large part is excreted unchanged, but in combination, by the urine (Curci). The activity of pilocarpine is destroyed by digestion with liver emulsions or serum; but active pilocarpine can be extracted from such mixtures by acidified alcohol. The inactivation is therefore probably an adsorption phenomenon. The "bound" alkaloid does not dialyze (Beutner, 1923) and is not precipitated by iodine (Jendrassik, 1923). The inactivating substance is not cholesterol or lecithin. Its quantity varies for the serum of different animals, the disintoxication occurring most readily in the serum of rabbits and least readily in dogs; with cat or ox serum intermediate (Storm van Leeuwen, 1918). Similar combinations apparently occur between rabbits' serum and other alkaloids; for instance, atropine, strychnine, procaine and cocaine (Beutner, 1923).

Symptoms of Poisoning.—The symptoms, which apply also to muscarine, begin with greatly increased secretion of saliva, sweat and tears; then nausea, profuse vomiting and painful diarrhea; pupillary contraction and spasm of accommodation; pulse variable in rate, tense and arrhythmic; palpitation; dyspnea with rales; sometimes confusion of ideas, vertigo, tremors and feeble convulsions. Death occurs either by paralysis of the heart or edema of the lungs. *Untoward effects* from the alimentary canal are seen most frequently if the drug is given by mouth, but occur also on hypodermic administration. They consist in prolonged and depressing nausea and vomiting, sometimes leading to collapse. The disturbance of accommodation causes misty vision. A burning sensation in the urethra, with sudden and irresistible desire to urinate, is often noticed. Atropine is a physiologic *antidote.* The general *treatment* of alkaloidal poisoning would be employed.

***Pilocarpine Nitrate**, U.S.P., is freely sol. in water (1:4). Dose, 3 to 12 mg., $\frac{1}{20}$ to $\frac{1}{5}$ grain. The *hydrochloride* is highly deliquescent and therefore undesirable.

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PHYSOSTIGMINE AND NEOSTIGMINE (PROSTIGMINE)

Physostigmine (also called *eserine,* from the native African name of the plant), an alkaloid of physostigma or "calabar bean," has been synthesized (by P. L. Julian and Pikl, 1935). It has a cholinergic action, chiefly by inhibiting the esterase that converts acetylcholine into the much less active choline. Its effects, therefore, correspond to those of parasympathetic stimulation, and it is a potent antagonist of atropine. Its powerful miotic action is employed in glaucoma, the stimulation of the intestines in intestinal paresis. Glandular stimulation is much less marked than with pilocarpine. It causes fascicular twitchings of striped muscle and is mutually antagonistic with curare. It is used in the treatment of myasthenia gravis. It is quite toxic by depression of the central nervous system, including paralysis of the respiration. It is employed as the salicylate. Solutions deteriorate on standing, turn brown and become more irritant. The characteristic sensitization to parasympathetic stimulation by inhibition of acetylcholine esterase is also produced by a considerable series of aromatic amine urethane derivatives (A. C. White and Stedman, 1931; N. W. Karr, 1942). The most important is *neostigmine* (*prostigmine*). Its somewhat lower toxicity is advantageous for systemic administration in myasthenia. Its intestinal potency is about equal to that of physostigmine; its miotic action is somewhat less.

Synergism of Smooth Muscle.—Fuehner, 1918, demonstrated on the ganglion-free smooth muscle of the *leech* body the remarkable potentiation by physostigmine of the stimulant action of acetylcholine (over 1,000,000 times) and to somewhat less degree of barium, while choline and pilocarpine are not potentiated at all by physostigmine. Guanidine acts like physostigmine, but is somewhat weaker.

Autonomic Antagonisms.—The inhibition of the augmentory actions by atropine is less complete for physostigmine than for acetylcholine, so that there is still some question whether physostigmine acts solely on the choline esterase (A. S. Dale and Narayana, 1935; Kahane and Levy, 1937). Physostigmine neutralizes the atropine action on the parasympathetic innervation of smooth muscle in practically all organs, but not the secretory paralysis of glands. It antagonizes the augmentor actions of epinephrine on the uterus, heart and blood vessels, but not the depressant action on intestines or on guinea pig uterus. It does not antagonize barium or posterior pituitary stimulations (K. Granberg, 1926).

Actions on the Eye.—Physostigmine causes constriction of the pupils (discovered by Fraser of Edinburgh, 1863), spasm of accommodation (near vision), twitching of the eyelid and lowering of the intra-ocular pressure. The intra-ocular actions are due to increased excitability of the oculomotor receptive mechanism. The effects of physostigmine can be removed by the application of atropine, and *vice versa;* but this requires much larger doses than does a normal eye. The localization was discussed in the general description of autonomic reactions.

The action on the pupil appears somewhat earlier and lasts somewhat longer than that on accommodation; on local application of a 1 per cent solution the *miosis* begins within ten minutes, reaches its maximum in thirty to fifty minutes, stays maximal for three or four hours and then disappears gradually in three or four days. The physostigmine contraction is greater than can be produced by strong light, although the physostigmine pupil contracts further even to weak light. With the maximal contraction, the pupil is generally irregular in shape. Physostigmine is much more effective in counteracting the mydriasis of cocaine than of atropine. *The spasm of accommodation* begins in about twenty minutes and passes off in about two and one-half hours, leaving the excitability somewhat increased. Through the contraction of the ciliary muscle, the lens becomes more spherical and objects appear enlarged and more distant. *The excised iris sphincter of mammals* is constricted by dilutions of 1:30,000, the intensity varying with the concentration. With 1:50,000, it dilates (D. R. Joseph, 1917). In the normal eye, physostigmine produces a slight fall (3 to 8 mm.) of *intra-ocular tension*, lasting some twelve hours (Luebs, 1913). The fall is more marked in glaucoma (Bollet and Curtil, 1911).

Permeability.—After intravenous injection of trypan red, this appears in the aqueous humor much more abundantly when the eye is inflamed or when physostigmine is applied. It is not influenced by atropine (P. A. Lewis, 1916). The potency of *local anesthetics* on rabbit's conjunctiva is diminished by neostigmine (Le Bow and Slaughter, 1945).

Therapeutic Use of Oculomotor Actions.—Physostigmine may be used to counteract effects of atropine, to break up adhesions of the iris and lens (in alternation with atropine); in the treatment of peripheral corneal ulcer; and to lower the intra-ocular pressure in *glaucoma.* The continued use of physostigmine or pilocarpine produces amelioration of the glaucoma symptoms, often more than iridectomy; but they are not curative (Posey, 1914). Witmer, 1921, states that strong solution (2 drops of 1 per cent) may provoke an acute attack of glaucoma in patients subject to the disease; while $\frac{1}{10}$ per cent solution tends to relieve attacks. Even this concentration may produce conjunctivitis if its use is long continued. Its action in *ulcer* is perhaps explained by contraction of the iris vessels.

Application.—Physostigmine is used locally, in 0.1 to 1 per cent solution of the salicylate (in glaucoma, generally 0.1 per cent, two to six times a day). Solutions of 0.5 per cent and higher sometimes cause considerable irritation and pain.

Intestines.—Therapeutic doses of physostigmine increase gastric and intestinal peristalsis. Toxic doses produce spastic contraction. The action is utilized in intestinal paresis (postoperative ileus, etc.): 2 mg. ($\frac{1}{30}$ grain) hypodermically (larger doses would be dangerous). Cannon and Murphy, 1907, showed that it has a marked effect, lasting, however, only a few hours. Acetylcholine has been added to increase the action (McCrae).

Colon movements, recorded from human colostomized patients by a balloon technic, are stimulated by 1 mg. of physostigmine, and more potently by neostigmine. The latter is markedly potentiated by pituitrin and by ergot (H. F. Adler and Atkinson, 1941).

In experimental *paralytic ileus* produced in dogs by intestinal obstruction, A. Ochsner, Gage and Cutting, 1930, found physostigmine the only substance that consistently raised the intestinal tone and motility (neostigmine was not tried). Pituitary, choline, acetylcholine and hypertonic sodium chloride solutions were ineffective. With excised rabbits' intestines, physostigmine produces large rise of tonus by parasympathetic stimulation, abolished by atropine. Larger doses paralyze the parasympathetic ganglia, and still larger doses the muscle (Heathcote, 1932). J. L. Law, 1940, reports considerable success from treating *megacolon* in children with parasympathetic stimulants.

Neostigmine against postoperative intestinal paresis is at least as effective as physostigmine, and somewhat less toxic. One cc. of 0.5:1000 solution is injected hypodermically on the day after the operation, and repeated in four to five hours if necessary. Its action is assisted by an enema. It is used similarly with *postoperative paresis of the bladder.* It generally produces fecal and urinary evacuation in about half an hour. It has relatively little action on the pupil, and in therapeutic doses on the circulation. Harger and Wilkey, 1938, advise prophylactic injection of 0.25 mg. at the time of operation, repeated every four to six hours, or every two hours if necessary.

Gastric movements in man are usually inhibited by *neostigmine*, but it increases them after atropine (Veach, Lauer and James, 1938). The volume and acidity of the *gastric juice* are increased (Necheles *et al.*, 1938).

Pharmacology of Neostigmine.—This was synthesized by Stedman, 1931, and investigated pharmacologically by Aeschlimann and Reinert, 1931, and clinically by Weigandt, 1931, and Carmichael *et al.*, 1934. It is less active than physostigmine on the eye and less depressant to the heart and blood pressure (0.1 mg. per Kg. had practically no effect); but 0.02 mg. per Kg., by vein, stimulates peristalsis, and 1:7,500,000 contracts the isolated intestine of rabbits. Its toxicity by hypodermic injection in rabbits is about four times greater than that of physostigmine. Aiazzi-Mancini, 1934, found that 1:100,000 increases the movement and tonus of the excised intestines of rats, antagonizes the epinephrine paresis and is inhibited by atropine. In *rabbits* it produces transient vasoconstriction, stimulation of the vagus and paralysis of the respiration. On *leech muscle* it is synergistic with acetylcholine and with barium.

Striped Muscle.—Physostigmine and neostigmine produce fascicular contractions and tonic contracture. Several distinct actions are involved:

(1) *Fascicular twitchings* of peripheral origin, *not* antagonized by atropine, increased by blocking the nerve with procaine, not abolished by section of the motor nerve (Harnack and Witkowski, 1876), but disappearing on degeneration of the nerve (Magnus, 1908; Langley and Kato, 1915). The action is, therefore, on the receptive mechanism. It is mutually antagonistic with curare (Pal and Rothberger) and with magnesium (Meltzer and Auer, 1906; Joseph and

Meltzer, 1909). Similar twitchings are produced by guanidine, barium, nicotine and by electric nerve stimulation in certain stages of fatigue (Langley, 1916; Langley and Kato, 1920). (2) *Tonus* in frogs, by peripheral action, through sensitization to acetylcholine, and antagonized by atropine. (3) *Tonus* in fowl, by direct muscular action, not prevented by atropine or by nerve degeneration (Edmonds and Roth, 1908). (4) *Coarser contractions of the muscles;* nystagmus and rhythmic movements of the nictitating membrane of cats. These are of central origin and are abolished by atropine. (5) *Increased work capacity* with diminished lactic acid production, in athletes as well as in excised frog muscle (E. Milla, 1939). (6) Large doses of physostigmine weaken the response of muscle in cats, both to direct and to indirect stimulation (F. W. Maurer, 1939).

In *warm kept frogs*, physostigmine and neostigmine produce no change in the main response to stimulation, except in after-tension after the shock (S. L. Cowan, 1940).

Direct Muscular Action.—When choline esterase has been inactivated by "DFP," skeletal muscles respond to arterial injections of neostigmine as they do to acetylcholine, suggesting that neostigmine acts directly on muscle, in addition to its inactivation of the esterase. Its chemical structure is also related to the choline esters; the latter, conversely, inhibit choline esterase (W. F. Riker *et al.*, 1946).

Motor nerves exposed directly to physostigmine or neostigmine show practically no change in action current, but lower stimulation-frequency suffices for contraction (S. L. Cowan, 1940).

In *myasthenia gravis*, neostigmine and physostigmine produce marked but transient improvement of muscular tonus (Mary B. Walker, 1934, 1935). The effect is noticeable in five minutes after hypodermic injection of 1.5 to 2.5 mg., becomes optimal in an hour and fades in six to eight hours. For continued treatment, 0.5 mg. of neostigmine may be administered hypodermically, or 15 mg. by mouth, beginning with three times daily. Viets, 1944, states the average daily maintenance dose as 163.5 mg. One patient took 375 mg. (25 tablets) daily for more than two years, without untoward effect. No tolerance is acquired. Ephedrine, potassium chloride, or guanidine is sometimes added. Neostigmine does not improve the muscle tonus in other neurologic conditions, so that it has some diagnostic as well as therapeutic value (A. M. Harvey and Whitehall, 1937; Gammon and Scheie, 1937). The effects agree with those of acetylcholine, and Dr. Walker introduced physostigmine on the assumption that myasthenia involves acetylcholine deficiency.

Intra-arterial injection of neostigmine into the brachial artery of *normal subjects* produces local paresis and fascicular twitchings. *In myasthenia* patients it causes almost immediate increase of grip strength, lasting three to five hours. Even high concentrations do not produce fascicular twitchings as in normal subjects. Intra-arterial injection of *acetylcholine* also produces transitory weakness in *normal* subjects. In *myasthenia* patients it causes sustained contracture of the injected muscle. *Epinephrine* increases the motor power, but much less than does neostigmine. *Ephedrine* by mouth results in moderate increase of muscle power (A. M. Harvey *et al.*, 1941). Destruction of choline-acetylase by intra-arterial injection of "*DFP*," (1.5 mg. in 3 cc. of saline into brachial artery) is similar to that effected by neostigmine, but the improvement of local strength is noticeable for eight to ten days (A. M. Harvey *et al.*, 1946).

These facts would suggest that myasthenia involves excess of choline acetylase, but this is not so The choline esterase content of muscle (M. S. Jones and Stadie, 1939) and of blood (A. Wilson and Stoner, 1944) is normal, but is lowered when physostigmine or neostigmine is administered (A. T. Milhorat, 1941). The serum and cerebrospinal fluid are less effective than normally in promoting acetylcholine synthesis *in vitro* (Torda and Wolff, 1944).

An alternative assumption is that myasthenia involves some curare-like factor that impedes the transmission of acetylcholine stimulation to the muscle, and that can be overcome by increasing the acetylcholine concentration, directly or by blocking the acetylase. Clinical observations suggest that this curaroid factor comes from *hypoplastic thymus*, for half of the myasthenia patients have demonstrable abnormalities of the thymus, and excision of this gland often results in prompt cure (Blalock, McGehee *et al.*, 1941; A. M. Harvey *et al.*, 1942).

Relief of "Muscle Spasm."—Neostigmine decreases the proprioceptive hyperirritability and incoordination of *poliomyelitis*, and partially relaxes the muscle spasm, relieving the pain and facilitating the use and training of the muscles. It was reported to give similar relief in rheumatoid *arthritis*, fibrositis and bursitis, in spastic hemiplegia and post-trauma disability, even if this has persisted for years. The action is not antagonized by atropine and is assumed to be directly on synapses in the spinal cord (Kabat and Knapp, 1943; H. Brainerd *et al.*, 1945; M. J. Fox and Spankus, 1945; A. Cohen, Trommer and Goldman, 1946). The results in rheumatoid arthritis have been disappointing, and over half the patients had alarming reactions (P. S. Hench, 1946; V. G. Baldoni *et al.*, 1946). Intrathecal injection of neostigmine in man produces loss of muscle tonus (M. Kremer, 1942).

Deafness is sometimes benefited by neostigmine (C. T. Davis and Rommel, 1939). The mechanism is not clear, and others have found no significant improvement in fairly extensive series of patients (Ersner *et al.*, 1941).

Bronchial Stimulation and Pulmonary Circulation.—Physostigmine contracts bronchial and tracheal muscle, with asthma-like dyspnea. It is claimed that the alveoli themselves are contracted, in contrast to histamine (J. Yamada, 1930), but this is difficult to conceive. Perfusion of physostigmine through the pulmonary circulation causes constriction of the pulmonary vessels as well as of the bronchi (A. S. Dale and Nasayana, 1935).

Systemic Circulation.—In man, therapeutic doses of physostigmine or neostigmine (0.5 mg. hypodermically) produce marked rise of skin temperature, lasting two to six hours, owing to arterial vasodilatation (Perlow, 1939). Toxic doses of physostigmine cause serious dizziness and faintness, without significant change in the heart rate (Robinson, 1915). The experimental data are somewhat complex (Heathcote, 1932). In general, *small doses* of physostigmine slow the heart rate in frog, rabbit and cat. They increase the T wave of the electrocardiogram (F. R. Miller *et al.*, 1940). *Moderate doses* potentiate vagus and acetylcholine stimulation (Verlot, 1936), and prolong but do not increase the acetylcholine fall of blood pressure (E. Zinnitz, 1936). The cardio-inhibiting carotid reflex is strongly sensitized (Van der Linden, 1932). *Large doses* paralyze the vagus ganglia or center. *Very large doses* produce systolic arrest by direct action of the cardiac muscle.

Sensitization to Choline and Acetylcholine.—Preliminary injection of physostigmine greatly intensifies and prolongs the effects of choline and acetylcholine on the circulation, both the vagal phase (slow heart and fall of blood pressure) and the sympathetic phase (quickened heart and rise of pressure; Viale and Martini, 1931). Small doses potentiate and large doses antagonize the pressor action of nicotine (F. W. Maurer, 1939).

The *blood pressure* tends to rise by strong vasoconstriction, partly through sensitization of the carotid sinus vasomotor reflex (Vercanteren, 1932), but chiefly by peripheral action mainly on the intestinal vessels (Dixon, 1903). It occurs on perfusion of the limbs of frog and cat and of the ear and kidney of rabbit. It is not prevented by atropine or ergotamine (T. Kunika, 1927). The action is, therefore, directly on the arterial muscle.

Neostigmine quickens the excised frog heart, but produces peripheral vagus slowing in dogs. It increases the blood pressure of cats, also after atropine, perhaps by increasing epinephrine output. In dog heart-lung preparations it slows the heart, decreases the total output and the coronary flow, with variable effects on the blood pressure (Mendez and Ravin, 1941). It has been reported useful against peripheral *vasospasm*, 7.5 to 15 mg. by mouth three times daily (Perlow, 1940).

Polycythemia; Contraction of the Spleen.—Physostigmine produces acute and considerable increase of the red cells and also of the total volume of the circulating blood (maximum in an hour, return to normal in two or three hours) (Nelson and Edmunds, 1923). This does not occur if the spleen has been excised, so that it is due to contraction of the splenic musculature (P. Testoni, 1930). The increased blood volume also contributes to the rise of blood pressure. The *coagulation time of the blood* is shortened by physostigmine, in dogs and rabbits (S. Marras, 1934).

Blood Sugar Level.—In rats, physostigmine produces marked rise of blood sugar. Atropine prevents this effect (Preobrazkenski, 1934; M. C. Hrubetz, 1937).

Epinephrine output is increased by physostigmine, in contrast to pilocarpine. The stimulation is central, for it does not occur after section of the nerves (Stewart and Rogoff, 1920).

Glandular Secretions.—Physostigmine stimulates the same glands as pilocarpine (except mammary; Ott and Scott, 1912); but the increase of secretion is much less marked, being counteracted by the vasoconstriction. Like other intestinal stimulants, physostigmine increases the elimination of *uric acid* (Abl, 1913).

Sweat.—Physostigmine provokes sweating of cat's paw. This is decreased or arrested by section of the nerves, so that the action is perhaps partly central (Langley and Kato, 1915).

Menstruation.—Neostigmine, 0.25 mg. intramuscularly, or 0.5 mg. of the methylsulfate, on three successive days almost invariably induces menstruation without untoward results in amenorrhea when this is not due to pregnancy, endocrine deficiency or gross pelvic disease. It is useful in treating temporary functional amenorrhea; but as a diagnostic sign of pregnancy it is unreliable, misleading, and sometimes causes abortion (Soskin, Wachtel and Hechter, 1940; A. Winter, 1940; Winkelstein, 1942).

Central Effects.—The action on the central nervous system is first tetanizing (Heubner, 1905), then rapidly paralyzing, *beginning*, at least in man, in the *lower portions*, so that *consciousness is preserved* to the end. The *respiration* is at first increased, due largely to stimulation of the afferent endings of the vagi, for the quickening is much less after the vagi have been cut. There are also other evidences of stimulation—excitement, etc.—but these have been considered *secondary to respiratory paralysis*, the central actions of the alkaloid being mainly depressing. It inhibits the knee jerk and depresses other spinal reflexes (Merlis and Lawson, 1939). Dyspnea is a marked symptom, due to paralysis of the respiratory center and spasm of the bronchial muscles (Harnack and Witkowski, 1876). The depressant action of physostigmine has led to its therapeutic trial in epilepsy, chorea, tetanus, etc., without much success. Neostigmine and acetylcholine depress spinal reflexes and inhibit strychnine convulsions, but physostigmine has the opposite effect (Schweitzer and Wright, 1937). In dogs, physostigmine decreases the minimal convulsive and lethal dose of *metrazol* and increases the intensity and duration of the convulsions. Pilocarpine does not have this effect (Gutierrez-Noriega, 1945). Neostigmine inhibits respiration. This may be preceded or followed by stimulation, the latter more marked in decerebrate animals (A. Schweitzer and Wright, 1938).

Neostigmine-Morphine Synergism.—Dr. Slaughter *et al.*, 1940, 1946, report that neostigmine doubles the analgetic potency of morphine clinically (0.5 mg. of the methylsulfate, hypodermically) and in cats. It produces a similar increase of analgesia with dilaudid and codeine, but not with monoacetyl morphine. H. L. Andrews, 1942, failed to confirm the potentiation, and the matter is in dispute.

Physostigmine Poisoning.—The *symptoms* are restlessness, weakness, nausea, vomiting, sometimes purging; epigastric pain; rarely miosis; salivation, lacrimation and sweating; palpitation with slowed pulse; dyspnea; muscular twitchings; convulsions; collapse. Death occurs by asphyxia, through depression of the respiratory center and by bronchial spasm (Schweitzer and Wright, 1938), with the reflexes preserved to the end. The fatal dose is not known. The location of the *emetic action* has not been definitely determined, because of the difficulty of fixing the emetic dose (Eggleston and Hatcher, 1915). *The treat-*

ment of physostigmine poisoning consists in evacuation, stimulants and atropine ($\frac{1}{2}$ to 1 mg.). Frazer found that small doses of atropine saved animals from three times the fatal dose of physostigmine, but that larger doses are synergistic; curare and magnesium are effective in the laboratory, but are dangerous for man.

Fate.—Physostigmine is not destroyed by frog's liver (Clark, 1912).

Neostigmine Poisoning.—Although 30 mg. by mouth do not produce untoward effects (Everts, 1935), even when repeated three times daily, 45 mg. by mouth cause toxic symptoms, identical with those of physostigmine. They may be quite severe. Goodman and Bruckner, 1937, report vagal bradycardia and salivation; then, three hours after the administration, sudden onset of collapse, great intestinal hyperactivity of a peculiar variety, fibrillary twitching of skeletal muscles, and miosis. Improvement began in an hour (atropine had been given). Consciousness was not disturbed. The minor toxic effects which sometimes occur in the clinical use are promptly relieved by atropine, 0.65 mg. ($\frac{1}{100}$ grain) under the tongue (Perlow).

Eseridine, another alkaloid of physostigma, acts similarly to physostigmine, but is only about a tenth as active (R. S. A. Heathcote, 1932).

PREPARATIONS.—***Physostigmine Salicylate,** U.S.P. (Eserine Salicylate), is soluble in water (1:75) and in alc. Dose, 0.6 to 2 mg., $\frac{1}{100}$ to $\frac{1}{30}$ grain. Watery solutions of Physostigmine salts (not the dry salts) oxidize under the influence of light, air and the alkali of glass vessels, acquiring a pink color (due to "rubreserine," Woelfflin, 1913). Such colored solutions should not be employed; Hallauer, 1899, states that they are more irritant. The decomposition products include rubreserine and eserine blue (with about a hundredth the potency of physostigmine on serum acetylcholine esterase), and the inactive eseroline and eserine brown (S. Ellis, Krayer and Plachte, 1944). The decomposition is retarded by the addition of a little boric acid.

***Neostigmine Bromide,** U.S.P., *Prostigmine bromide*, is a white, crystalline powder, freely sol. in water (1:1), relatively nonhygroscopic; used orally for the treatment of myasthenia gravis, as the *Neostigmine Bromide Tablets*, U.S.P., usually 15 mg., three times daily (the dosage may be doubled cautiously, if necessary).

Neostigmine Methylsulfate, U.S.P., sol. in water (1:10), is used hypodermically as the *Neostigmine Methylsulfate Injection*, U.S.P., in water for injection, usually available in ampuls of 0.25 mg. and 0.5 mg. in one cc. For prevention of *postoperative distension* 0.25 mg. is injected every four to six hours, beginning twenty-four hours before the operation; for treatment of this condition, 0.5 to 1 mg.; for myasthenia gravis, 0.5 mg.

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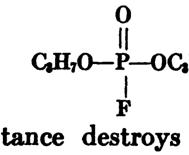
DI-ISOPROPYL FLUOROPHOSPHATE, "DFP,"



$$C_3H_7O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle F}{|}}{P}}-OC_3H_7$$

This substance destroys choline esterase irreversibly, so that its administration decreases profoundly the choline acetylase activity of the blood plasma and muscle for several weeks after a single administration, although it returns eventually as new esterase is formed. It relieves the muscle weakness of myasthenia gravis less completely but more persistently than neostigmine (Comroe, Todd *et al.*, 1946). It relieves glaucoma more often than physostigmine (review, A. Gilman, 1946).

Sodium fluorophosphate also inhibits choline esterase, but alkyl groups which render it fat soluble, greatly increase its action.

Serum choline esterase is especially susceptible to DFP, so that it may be destroyed by doses which leave that of other tissues practically intact. Synaptic transmission and the functions of muscle and nerve tissues are not inhibited until a dosage is reached which destroys nearly 80 per cent of their choline esterase. Conduction in the nerve fibers themselves is not affected by complete destruction of their choline esterase (Crescitelli, Koelle and Gilman).

The regeneration of choline esterase of serum requires a few weeks; several months are necessary for the brain and muscle.

Injected into the brachial artery, 1.5 mg. of DFP in 3 cc. of saline, produce the same effects as acetylcholine or neostigmine: diffuse sweating of the forearm and hand, numerous spontaneous fasciculations, pronounced motor weakness. A single nerve stimulus gives the normal voltage of muscle potential, but the response becomes repetitive. The effects reach their height in thirty to forty minutes and are still detectable after 120 hours.

DFP inhibits the action-potential for direct stimulation of curarized skeletal muscle (R. Couteaux *et al.*, 1946).

The effects in *myasthenia gravis* patients are the same as with neostigmine: striking localized increase of muscular strength, perceptible for eight to ten days; no fascicular twitchings. The improvement of motor power does not occur if neostigmine was injected just prior to the DFP (A. M. Harvey, Jones *et al.*, 1946).

Continued administration of therapeutic doses does not result in significant damage. *High doses* produce nicotinic fibrillation, transient muscarinic signs (bronchial constriction, salivation, diarrhea), persistent urinary incontinence, hindleg paralysis; cardiospasm with extreme esophageal distention, leading to death by starvation (G. B. Koelle and Gilman, 1946).

Physostigmine protects choline acetylase from inactivation by DFP *in vivo*, and gives considerable protection against the toxic effects of DFP, provided that this is administered in advance. Physostigmine with atropine saves from thirty times the LD_{50}. If the DFP, however, is injected first, it sensitizes to physostigmine. The sensitization persists for months after the choline acetylase has returned to normal. DFP also sensitizes to future administration of DFP (R. Koster, 1946).

Conjunctival instillation of 0.1 to 0.2 per cent DFP in normal men produces miosis lasting six to twenty-seven days, and decreased intraocular tension for four to eight days, without local irritation. It overcomes and outlasts the cycloplegic action of atropine and homatropine. In *glaucoma* it is more often effective than physostigmine and pilocarpine, and needs less frequent application. *Undesirable effects* are visual blurring, brow and eyeache, spasm of accommodation and pericorneal congestion (Leopold and Comroe, 1946).

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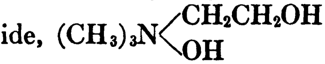
CHOLINE AND CHOLINE ESTERS

Acetylcholine is important as the parasympathetic neurohormone. It is rapidly hydrolyzed by the choline esterase of the blood and tissues into the much less active *choline*, trimethyl-oxyethyl-ammonium hydroxide,  $(CH_3)_3N\langle^{CH_2CH_2OH}_{OH}$. This occurs as a constituent of lecithin probably in all animal and vegetable tissues. It is doubtful whether it exists free in the living tissues, in detectable quantity. Choline and its derivatives have *three distinct actions* (Dale, 1914) which vary independently in relative degree in the different derivatives: (1) parasympathetic stimulation ("*muscarinic action*"), which lowers blood pressure of nonatropinized cats; (2) "*nicotinic action*," which stimulates autonomic ganglia and many myoneural functions, including skeletal muscle, in small concentrations; and depresses them in high concentrations (Rosenblueth and Simeone, 1938). It raises the blood pressure of atropinized cats, and also produces contracture of denervated gastrocnemius of the cat; and (3) *epinephrine mobilization*, resulting in dilatation of denervated and atropinized iris. These actions are also produced by other *quaternary ammonium bases, arsonium* and other compounds of this general structural pattern (Reid Hunt and Renshaw, 1933). Numerous esters of choline have been prepared, and studied pharmacologically, especially by Reid Hunt and his associates. They may be discussed together, as their actions are qualitatively identical, but they differ greatly in potency, in the relative prominence of the three types of effects and in stability and, therefore, duration of action. Acetylcholine itself is unstable and its action brief. Its derivatives generally act by liberating acetylcholine (Renshaw *et al.*, 1938). Acetyl-beta-methylcholine (*methacholine*, "*mecholyl*") is stable enough for therapeutic use, intramuscularly as a brief but powerful parasympathetic stimulant, to slow the heart in tachycardia, to dilate the blood vessels in high blood pressure, and locally by electrophoresis for ulcers and arthritis; and more doubtfully for gastro-intestinal motor and secretory stimulation.

The *sensitivity to acetylcholine* is greatest for vasodilatation, then, successively, adrenal secretion, splenic contraction, respiratory acceleration. Cardiac inhibition requires relatively large doses (Tournade and Chardon, 1939). The most sensitive *test object* is physostigminized leech muscle, which detects 0.002 mg.; the Straub frog heart and the mouse intestine show 0.010 mg. (Gaddamer, 1936). Small intact earthworms are reported as sensitive as leech muscle (Gavrilesco and Ionesco, 1940).

Historical.—Choline was first isolated by Strecker, 1849, from bile; in 1862 he established its chemical constitution (G. A. Alles, 1934—reviewed). Acetylcholine was first prepared by von Baeyer in 1867. It was isolated from animal tissues by Dale and Dudley, 1929.

Distribution of Choline.—Choline and acetylcholine are the only forms which have been isolated from animal tissue and chemically identified. Choline may be assayed by conversion into acetylcholine and this by bio-assay, first suggested by Hunt and Taveau, 1906. Normal serum contains 2 to 20 mg. per liter (Hunt, 1915). About the same concentration exists in amniotic fluid; somewhat more in the urine and in cardiac and skeletal muscle; much less in cerebrospinal fluid and saliva. The proportion in the blood or cerebrospinal fluid has not been found increased in any pathologic conditions examined in man. No extra amount is liberated in anaphylaxis (S. Farber *et al.*, 1944). It has been reported increased by removal of the suprarenals, but the evidence is not decisive and does not prove a causative connection (Hunt, 1915). *Acetylcholine* is reported to occur regularly in the gastric juice of man and dog (E. Bloch and Necheles, 1938). It was demonstrated in ergot by Ewins, 1914.

Extraneous Sources of Choline.—Choline may be liberated from lecithin by putrefaction or autolysis. It therefore occurs in organ extracts, in many vegetables (Schulze and Trier, 1912) and in certain drugs (especially ergot). It may be formed in intestinal putrefaction, but it is readily destroyed by the intestinal bacteria and is less toxic than the analogous neurine and various amines which are also formed in putrefaction. Choline is but slightly toxic on hypodermic injection.

Fate.—Choline is largely destroyed in the body (v. Hoesslin, 1906). Its oral or hypodermic administration does not increase the amount in the urine, and intravenous injection does so but little (Guggenheim and Löffler, 1916), although it disappears rapidly from the blood stream (Hunt, 1915). After oral administration only 3 per cent of the choline can be recovered from the tissues; with intravenous, about 50 per cent, the greater proportion from the skin (Ellinger, 1914). It is not detroyed by blood *in vitro* (Wrede *et al.*, 1929). The destruction occurs largely in the liver, where the alcohol group is rapidly oxidized by an oxidase specific for choline (F. Bernheim and Webster, 1934). A part of the methyl is probably oxidized to formic acid, the remainder to CO_2 and water. No trimethylamine is formed (H. Fuchs, 1938). *The stability of acetylcholine* in aqueous solution was studied by Demole, 1930.

Acetylcholine esterases hydrolyze the ester in the tissues (Stedman *et al.*, 1932). Their concentration is especially high along the surface of the axons (Nachmansohn, 1941). Choline acetylase is inhibited by physostigmine, neostigmine and related substances, and to a less extent by a variety of other substances, including fluoride, antipyrine and other pyrazolones (E. A. Zeller, 1942). The physostigmine and neostigmine inhibition is a reversible balanced reaction, competing with acetylcholine for the surface of the enzyme (G. S. Eadie, 1942). Neostigmine is more effective than physostigmine (Babkin *et al.*, 1942). It is destroyed by "DFP" (see Index).

Choline Derivatives.—Hunt and Taveau, 1906 to 1911; Hunt, 1915; Ewins, 1914; Dale, 1914; and Simonart, 1932, investigated the relative toxicity and circulatory effects of a large series of choline derivatives. The substitution of OH in choline generally increases its activity, often greatly (Dale). The introduction of the acetyl radical increases the depressor effect 100,000 times, the toxicity only three times (Hunt). The correlation of the pharmacological actions with the physicochemical properties was attempted by von Oettingen and Bowman, 1933.

Choline antagonizes the acute toxicity of its triethyl analogue (A. S. Keston and Wortis, 1946).

Neurine, trimethyl vinyl ammonium hydroxide, may be formed from choline by bacteria. Its actions are similar to those of choline, but much stronger (Pal, 1911); it is far more toxic (Lohmann, 1911).

Betaine, trimethyl glycocoll anhydride, is nearly inactive by mouth; hypodermically, it acts similarly to choline. It is nontoxic (Velich, 1914); even 2.4 Gm. per kilogram by vein, in the rat, are harmless. It is excreted unchanged, and is therefore not a food (Andrlick, Velich and Stanek, 1902). The preparation and properties of its salts are described by Stolzenberg, 1914. It may be assayed by the response of striped, cardiac or smooth muscle, after conversion into its crotonic methyl ester (E. Strack and Fösterling, 1942). Betaine hydrochloride dissociates in solution, and has been utilized as a means of administering loosely bound hydrochloric acid. The dose, 0.5 Gm., corresponds to about 1.1 cc. of official Dilute Hydrochloric Acid.

Sulfonium Compounds.—The substitution of sulfur for the nitrogen of choline and betaine esters does not greatly alter their actions. In some cases there is considerable increase of the paralyzing nicotinic and curare actions. The addition of oxygen to the sulfur (sulfonyl compounds) greatly diminishes the potency (Hunt and Renshaw, 1932).

Acetyl-beta-methylcholine (Methacholine Chloride, Mecholyl) is closely related to acetylcholine. It produces practically no "nicotinic" action, *i. e.*, no stimulation of the sympathetic ganglia and no rise of blood pressure, but causes strong parasympathetic stimulation, *i. e.*, cardiac inhibition; peripheral vasodilatation involving most of the blood vessels, with fall of pressure; and stimulation of gastric and intestinal peristalsis.

Acetylcholine in small intravenous doses produces muscarinic effects (parasympathetic stimulation, antagonized by atropine). Nicotinic effects (rise of blood pressure after atropine) require much larger doses (Hunt and Taveau, 1911; Simonart, 1932). The effective dosage varies considerably in the same tissue; in frogs' heart, for instance, the minimal effective concentration ranges from 10−8 to 10−6 (Fuehner, 1923).

The *chief difference between mecholyl and acetylcholine* and most other choline esters is that the mecholyl hydrolyzes more slowly, in solution and in the tissues, and its action is therefore more lasting, although still brief: with intravenous injection, the effects on the heart and blood pressure last about a minute, those on the gastro-intestinal tract for ten to twenty minutes. The intensity of the actions is about the same with intravenous injection of equal doses of acetylcholine and mecholyl; but with hypodermic and oral administration, mecholyl is more effective.

Ethyl-beta-methylcholine acts similarly to the acetyl-beta-methyl choline. It is more stable, but somewhat less potent (J. Starr *et al.*, 1933).

Carbachol (*Doryl, Lentine*) is a relatively stable derivative, carbamylcholine chloride, with similar actions (Kreitmair, 1932; Dautreband, 1933; Velten, 1933). It is used locally in the eye for parasympathetic stimulation. Its intramuscular injection has caused fatalities (J.A.M.A., 1943, *123:* 1051).

Historical.—*Acetyl-beta-methylcholine* was first prepared by Taveau, 1909, and its pharmacology investigated by Hunt and Taveau, 1911, and subsequently by Simonart, 1932; Comroe and Starr, 1933; and others. Its clinical introduction is due chiefly to Starr and his associates, 1933. The earlier work entailed some confusion between the alpha and beta homologues, which was cleared by Major and Chite, 1932. Hunt and Renshaw, 1934, point out that their pharmacologic results of 1911 show that they had worked with the beta, since the alpha produces more pronounced nicotinic effects.

Response of Normal Human Subjects to Acetyl-beta-methylcholine.—The following phenomena are reported by J. Starr *et al.*, 1933, and Myerson *et al.*, 1937: Within a minute after the hypodermic injection of 20 or 30 mg. of mecholyl, the face, neck and chest become flushed. This is followed by generalized sweating, salivation, rhinorrhea, lacrimation, slight or moderate fall of blood pressure; increase of pulse rate lasting a few minutes and often followed by slowing, generally with transient sinus arrhythmia; rise of cerebrospinal blood pressure. The effects last several minutes. They can be prevented by atropine. One subject in the twenty studied by Starr developed a typical and rather alarming asthmatic attack; three others had a sensation of substernal constriction. *Oral administration* requires 50 to 100 times the hypodermic dosage to produce significant effects, and the symptoms are milder and develop more gradually. The *nasal mucous membrane* absorbs mecholyl rapidly, with the same phenomena, including a precipitate fall of blood pressure lasting three to sixteen minutes (Van Dellen *et al.*, 1937).

Response of Normal Human Subjects to Acetylcholine.—The phenomena reported by Carmichael and

Fraser, 1933, differ but slightly from those described for acetyl-beta-methylcholine: *Intravenous injection* of 10 to 30 mg. (in forty-six subjects) was followed in a few seconds by abrupt slowing of the heart, a sensation of obstructed breathing leading to increased rate and depth of respiration, a burning sensation in the throat and the desire to cough. These last only a few seconds and are followed by quickening of the heart above normal, flushing of the face and neck, a sensation of heat and sometimes palpitation. This second phase passes off more gradually, but the whole reaction is over in half a minute. The blood pressure falls as the pulse slows and rises a little above normal when the pulse quickens. The degree of response varies in different subjects. It can be intensified by the previous injection of physostigmine and abolished by atropine, not by epinephrine.

Continuous Intravenous Injection.—L. B. Ellis and Weiss, 1932, found (on seventeen normal human subjects) that acetylcholine has to be injected at the rate of 20 to 60 mg. per minute to maintain definite but minimal effects. The maximum tolerated rate was 90 to 140 mg. per minute. This therefore represents the rate of destruction. The larger doses caused nausea and emesis. The blood pressure was generally unaltered. The largest tolerated quantity injected amounted to 1 Gm. in ten minutes. Man appears to be more tolerant than animals. *Hypodermic injection* is much less effective, requiring about 200 times the dosage of intravenous injection, or of intramuscular mecholyl (L. Weiss and Ellis, 1934). *Intra-arterial injection* produced marked regional vasodilatation, lasting half an hour after injection, so that the destruction was much slower than with intravenous injection (Ellis and Weiss).

Toxic Dosage of Choline.—With ordinary slow venous injection, cats show no toxic effects after 15 mg. per Kg.; 30 mg. produce reversible arrest of respiration; 35 mg. per Kg. are fatal. As the choline is rapidly destroyed, 0.8 to 0.9 mg. per Kg. per minute (as 0.2 to 0.4 per cent) may be injected practically indefinitely (Arai, 1922). Neostigmine greatly increases the response to mecholyl, and may lead to dangerous cardiac collapse (Myerson, Rinkel *et al.*, 1937).

Cardiac Inhibition.—Choline and its esters weaken and slow the heart by vagus stimulation, central and peripheral (Hunt, 1915). Doses of acetylcholine too small to stimulate directly increase its sensitivity to electric stimulation. Large doses (0.2 to 10 mg. per Kg.) produce transitory stimulation, followed by marked and lasting decrease of response to electric stimulation (Barone, 1932). Intravenous injection of 0.25 to 2 mg. of mecholyl into dogs, 0.12 to 0.2 mg. in rabbits, causes auricular fibrillation or auriculoventricular block; also after section of the vagi (Iglauer *et al.*, 1941). The cardiac inhibition occurs in the *embryonic heart* only after the inhibitory nerve fibers have connected with the muscle (Armstrong, 1935), and does not occur even after physostigmine in the adult ventricle of fish, turtles and mammals, which is not directly innervated by the vagus (Garrey and Chastain, 1937). In the frog, segments from the different levels are inhibited about equally, so that all levels receive vagus innervation (Garrey and Bass, 1934). The site of the inhibitory action of acetylcholine appears to be on the *cell surface*, for its action on the frog heart is antagonized by *methylene blue*, which has been shown to act on the surface of the cells (R. P. Cook, 1926); and its action in the perfused frog ventricle is completed in a few seconds and can be removed by washing in a short time; nor is there any evidence of its accumulation by storage within the cells. The action is diminished by increase of Ca, K or OH in the Ringer fluid (A. J. Clark, 1927). The *oxygen consumption* is decreased by acetylcholine, even in the previously arrested frog and turtle heart (A. J. Clark, 1935). In dogs, also, small doses of acetylcholine decrease the oxygen consumption of the heart disproportionate to the reduction of the output (Gremels, 1936).

Other Cardiac Actions of Acetylcholine.—Vagus inhibition is ordinarily dominant; when this is prevented by atropine, the perfused heart of frogs (Barlow, 1928) and mammals shows stimulation of the sympathetic accelerator mechanism, which is abolished by ergotamine (R. J. S. McDowall, 1946). The perfusate relaxes rabbit intestine, indicating that acetylcholine liberates epinephrine in the heart (F. Hoffman *et al.*, 1945). Acetylcholine and atropine are mutual antagonists within a limited range, but higher concentrations of both give additive depression. Epinephrine in low concentrations counteracts the depression, but higher concentrations are also additive (Barlow, 1928). Continued *daily injections* of large doses of acetylcholine in rabbits lead to *focal necrosis of the myocardium* analogous to the degenerations in other organs (Henlein, 1939).

Anaphylactic Relations.—The guinea pig heart during anaphylactic shock liberates a cholinergic substance which inhibits the frog heart, probably in consequence of vagus stimulation. It is antagonized by atropine; but as it is not active on leech preparations, it is not acetylcholine (Went and Lissák, 1936). Sensitization of guinea pigs by protein injection causes their heart to respond to much greater dilutions of choline. This returns to normal with desensitization (Lissák and Went, 1936).

Cholines in Cardiac Therapy.—Vagus stimulation by choline was used by Boden and Wankell, 1928, with good results against paroxysmal tachycardia; to retard auricular flutter; in occasional dissociation of auricles and ventricles; and sometimes in auricular fibrillation. *Methacholine* (*mecholyl*) was introduced for the same field by Starr, 1933. In selected cases of paroxysmal tachycardia, which may have resisted other medication, the hypodermic injection of 30 mg. of mecholyl restores the normal rhythm, after a brief period of irregularity. For prophylaxis it is generally less efficient than quinidine. It is generally ineffective with other forms of tachycardia and with auricular fibrillation.

It is advisable to begin with small doses, 10 mg. of mecholyl hydrochloride hypodermically, increasing cautiously to 25 mg.; or 0.2 to 0.5 Gm. by mouth; both two or three times daily. Intravenous injection is dangerous and should not be used. If the effects are excessive, atropine may be administered (report, Council on Pharmacy and Chemistry, 1941, J.A.M.A., 117:*193*, 860; P. W. Morgan, 1943). Mecholyl is contraindicated in patients with bronchial asthma, coronary sclerosis, or with any severe illness.

Mecholyl may convert the auricular flutter into auricular fibrillation and thus slow the rate. The production of auricular fibrillation has been observed in several thyroid patients with previosuly normal hearts. It was of short duration (Nahum and Hoff, 1935). In patients in whom 0.1 mg. of *epinephrine*, intravenously, produced ventricular rhythms from numerous foci, this was prevented by the usual dosage of mecholyl (Nathanson, 1935). Hypodermic injection of 25 mg. of mecholyl into cats prevented ventricular fibrillation and death from electrocution which was fatal to control animals (Hoff and Nahum, 1935). Intracardiac injection of acetylcholine generally arrests electrically induced fibrillation of excised and perfused mammalian heart (R. Frölicher, 1945).

Blood Pressure Response to Choline and Its Esters.—The normal response is a considerable fall, due chiefly to a peripheral (parasympathetic) vasodilator action. In normal persons, 2.5 mg. of mecholyl hypodermically have little if any effect on blood pressure; in nearly all *hypertensive patients* this causes moderate to marked fall, generally with increase of pulse rate proportional to the fall of pressure (D. E. Engle and Binger, 1939). *In atropinized animals*, choline and acetylcholine produce a rise of pressure, a "nicotinic" action involving increased output of epinephrine; and probably stimulation of the vasomotor ganglia with larger doses. These nicotinic effects are slight with mecholyl.

Therapeutic applications of the vasodilator action have been tried against hypertension and in Raynaud's disease, without much success. H. Goldblatt, Kahn and Lewis, 1942, found it ineffective against experimental renal hypertension. It has been employed against vascular spasm from exposure to cold (0.05 to 0.1 Gm. by mouth). In obliterative arteriosclerosis, carbachol improved the rest-pain, but none of the other features (Saland *et al.*, 1945). In arthritis, mecholyl is carried to the joint by local *ion transfer*, moistening the positive pole with 0.2 to 0.5 per cent aqueous solution; but this has caused toxic systemic reactions, since the dosage is difficult to control. It is more useful in treating ulcers. The blood flow through the hand may be increased to more than five times the normal (H. Montgomery *et al.*, 1938). *Intra-arterial injection* of acetylcholine, 0.01 to 10 mg., or of mecholyl, 0.0001 to 3 mg., into the brachial artery of man produces marked vasodilatation of the arm and hand, without systemic effects (Myerson, Loman *et al.*, 1938). Cragg, 1936, reported encouraging results in tobacco amblyopia (more rapid improvement of vision) from the daily intramuscular injection of 15 mg. of acetylcholine. *Exophthalmos* may result mechanically from distention of the blood vessels of the orbit (C. E. Brunton, 1940).

Variability of Response.—Choline generally lowers blood pressure (Mott and Halliburton, 1897), but sometimes there is, instead, a rise of pressure. In cats, the rise generally follows the fall (Pal, 1911). The variable response does not depend upon impurities (Renshaw, Underhill and Mendel, 1912). The result is influenced by the dose, anesthetic, and other conditions (Abderhalden and Mueller, 1911). The fall predominates if the blood pressure has been high (Benelli, 1914); in protracted ether narcosis, and after some sorts of curare. It counteracts the epinephrine rise (Gautrelet, 1909). The *pressor effect* is more prominent in light anesthesia or after section of the medulla (Pal, 1911).

Mechanism of the Blood Pressure Fall.—Peripheral vasodilatation is the most important factor (Hunt, 1918). With acetylcholine there is intense dilatation of the vessels of most organs, including the skin; relatively feeble in the splanchnic area in comparison with the nitrite fall; doubtful in the kidneys; absent in the lungs. Larger doses are constrictor. This dilator effect is more powerful than that produced by any other method. It is diminished or prevented by atropine, but synergized by physostigmine. It does not involve any of the known vasodilator paths, sympathetic or parasympathetic, or the posterior roots. It is different both from epinephrine and nitrite dilatation, which are not antagonized by atropine (Dale and Richards, 1918).

Large doses of acetylcholine produce pulmonary edema and occasionally splenic edema, similarly to anaphylactic shock (R. Altschul and Laskin, 1946).

The *rise of blood pressure*, which occurs when the dilator receptive mechanism has been paralyzed by large doses of atropine, is due to increased output of epinephrine, exclusively so with small doses (Feldberg and Mintz, 1931); larger doses appear to stimulate the arterial muscle directly, for they raise the pressure after excision of the adrenal gland, and they constrict the vessels of atropinized excised or perfused organs (R. Hamet, 1934).

Special Vascular Beds.—The coronary blood flow is reported as first increased, then diminished, in rabbits, dogs and cats, by acetylcholine and mecholyl (Wedd, 1926). In the arrested dog heart, acetylcholine produced coronary dilatation (Katz and Londner, 1939). In the perfused cat heart, the coronary flow is diminished (Orczechowski, 1933). The *pulmonary arterioles* are slightly dilated by acetylcholine (Daley and von Euler, 1932, perfusion, dogs), the bronchiolar vessels are constricted (A. S. Dale and Narayana, 1935). Microscopic sections of pulmonary arteries are constricted by mecholyl (Gilbert, 1938). The *cerebral vessels* are dilated by acetylcholine, with rise of cerebrospinal pressure. The *portal vessels* are constricted by large doses of acetylcholine and unaffected by smaller ones (McMichael, 1933, cats). The *carotid artery* of rabbits is relaxed by mecholyl (Sollmann and Gilbert, 1937). The *spleen* is contracted by acetylcholine, clinically as well as in animals. This is prevented by atropine (Bouyoucos, 1932; Gotsev, 1936). The *lymph flow from the thoracic duct* is briefly increased by acetylcholine (Beznak, 1937). *Thio-esters of choline* produce rise of blood pressure, not abolished by atropine. The rise stimulates the carotid sinus to bradycardia and hyperpnea. The action is brief (W. F. Alexander *et al.*, 1938).

Gastro-Intestinal Tract.—Choline and its esters produce parasympathetic stimulation of the tonus and peristalsis of the stomach and intestines, similar to pilocarpine and physostigmine, but generally milder. They increase the secretions innervated by the parasympathetic, especially the saliva and the gastric acidity. Their therapeutic usefulness is questionable.

Submaxillary secretion is increased by acetylcholine even when the intravascular pressure is kept constant (by perfusion, in dogs). The action is therefore direct. The increase of acid secretion is much greater with fractional doses; a single large dose causes scanty secretion of low acidity; the pepsin concentration is high in both. The effects on pyloric and fundal pouches are described by G. W. Stavraky, 1943. Mecholyl is prevented by atropine. Small doses of pilocarpine increase the response, large doses are antagonistic. Acetylcholine is not effective if the gland has been exhausted by previous stimulation of the chorda tympani (Anochin, 1929).

Clinical Effects of Mecholyl on Digestive Tract.—In normal men, this increases the *gastric acidity*, but less than histamine, and with more systemic disturbance. It increases the *gastric motility* if the stomach is filled, but arrests the hunger contractions of the empty stomach. It increases peristalsis of the *small intestine*, but not constantly in the colon. It has been tried in *postoperative abdominal distention*, sometimes with symptomatic relief (W. O. Abbott), but its value is questionable. Patients with *atonic colon* are reported to respond to the hypodermic injection of 30 mg. of mecholyl with one or two imperative evacuations, within thirty minutes, and three or four within twenty-four hours (Myerson, Schube and Ritvo, 1937).

Acetylcholine on Gastric Acid Secretion.—Single intramuscular injections of 0.3 to 0.4 Gm. have little effect, but repeated doses give a moderate increase. Some hypochlorhydria patients, and rarely those with achlorhydria, were restored to normal acidity by a series of injections (Faroy and Deron, 1931). Necheles *et al.*, 1938, report increase of gastric secretion, volume, acidity and pepsin, in man and dogs. L. S. Goodman, 1938, reports that this is especially marked with another ester, "Doryl." Mecholyl and pilocarpine inhibit the secretion of acid. This occurs with smaller doses if the drugs are injected into the lateral ventricles of the brain. Atropine antagonizes the anacidity (Ferguson and Smith, 1935).

Choline on Peristalsis.—X-ray observations on cats after slow intravenous injection of 5 to 10 mg. per Kg. show that the increased peristalsis is of the normal type and not spasmodic. The stimulation persists for hours. The large intestines are relatively little affected (Le Heux, 1921). The contractions are antagonized by epinephrine as well as by atropine (Bernheim, 1933). Choline injection was found to remove the gastro-intestinal paralysis produced by prolonged chloroform anesthesia (von Kuhlewein, 1921), or by peritonitis through laparotomy and handling, or through the intraperitoneal injection of iodine (Arai, 1922). Adequate observations on animals other than cats are lacking. Magnus, 1925, proposed for *clinical use*, the intravenous injection of choline, 0.6 mg. per Kg. per minute, for seventeen minutes. However, the formation of decomposition products may greatly increase the toxicity, so that caution would be necessary. Properly prepared ampuls do not deteriorate. Weiland, 1912, showed that saline solutions in which intestines have been immersed extract a stimulant substance from the serous coat. Le Heux, 1918, identified this as choline and showed that its removal from the intestines decreased their excitability and their response to atropine. He assumed that choline serves as a normal "*peristaltic hormone;*" and that the cathartic action of the salts of organic acids is due to the synthesis of powerful choline esters (1921). *The gallbladder* is stimulated to contraction by mecholyl (J. Flexner *et al.*, 1938).

Sweat.—Mecholyl provokes profuse alkaline perspiration, which is arrested by atropine, increased by pilocarpine and by neostigmine, not materially affected by epinephrine. The action is peripheral (Myerson *et al.*, 1937). Acetylcholine, 1:1000, intradermally, causes local sweating, less in women than in men. This is weakened or abolished by sympathectomy (D. Kahn and Rothman, 1942).

Bronchioles.—Acetylcholine causes marked contraction in perfused lungs (A. S. Dale and Narayana, 1935), and mecholyl does so in lung sections (Sollmann and Gilbert, 1937). In intact and atropinized animals, acetylcholine dilates the bronchioles by mobilizing epinephrine from the adrenal glands (Melville, 1938).

Respiration.—Acetylcholine produces successively stimulation, inhibition and again stimulation. The stimulation is due to stimulation of the carotid sinus; the inhibition is exerted directly on the respiratory center (A. Schweitzer and Wright, 1938). Direct application to the fourth ventricle increases respiration, and physostigmine sensitizes to this action (Worzniak and Gesell, 1938).

Uterus.—Choline and its esters produce contractions (Starr, 1933).

Urinary Bladder.—Choline and acetylcholine cause prolonged tonus which is antagonized by epinephrine and by atropine. Good results have been reported in postoperative bladder atony (Marsalek, 1933).

Skeletal Muscle.—In *frogs*, dilute solutions (1:100,000) of acetylcholine decrease the height of contraction and prolong the relaxation, similarly to fatigue (W. R. Hess and Rehsteiner, 1926). Higher concentrations produce a contracture, which is antagonized by atropine, not by curare (Riesser and Neuschloss, 1921). It is not accompanied by increase of lactic acid, as are the contractures of quinine, ammonia or potassium (Zondek and Matakas, 1927). Acetylcholine contracture of toad muscle liberates potassium into K-free Ringer perfusion fluid (Cicardo and Moglia, 1940). *In mammalian muscle*, especially the diaphragm and ocular muscles, acetylcholine produces prompt and brief contraction, more marked after degeneration of the motor nerve (Heidenhain). The contracture is not due to parasympathetic stimulation and is not affected by atropine, but is abolished by curare more readily than is the response to nerve stimulation (G. L. Brown, Dale and Feldberg, 1936; Simonart and Simonart, 1935). Vertebrate skeletal muscle, leech muscle and the body wall muscle of earthworms and other annelids are relatively insensitive to acetylcholine alone, but the response is greatly potentiated by *physostigmine* and nicotine. Mammalian intestinal muscle is much more sensitive to acetylcholine and not greatly potentiated by physostigmine (K. S. Wu, 1939). Choline and acetylcholine have no effect on peripheral *nerve fibers*, even in 0.1 mg. concentration (Lorente de No, 1944).

Acetylcholine Content of Skeletal Muscle.—A substance with the actions of acetylcholine has been demonstrated in muscle extracts. Its amount is notably greater in muscles that normally have a "tonic" function and are normally more susceptible to acetylcholine tonus; for instance, the clasping muscles of the forearms of male frogs, and the extrinsic eye muscles in mammals. Decerebrate rigidity does not increase the acetylcholine content of muscles (F. Plattner, 1932). Choline esterase is 10,000 times more concentrated about the motor endings than in the nerve-free portions of toads' sartorius muscle (Feng and Ting, 1938).

The cerebral motor cortex is stimulated by direct application of 5 to 10 per cent acetylcholine solution, producing epileptic convulsions in dogs (Moustaché and Dias, 1941), and electric potential changes resembling grand mal seizures. These are sensitized by prostigmine, $\frac{1}{20}$ to 1 per cent, and abolished by dilantin (Merritt and Brenner, 1941). Central effects of acetylcholine, atropine and physostigmine have been studied with arterial injection into decerebrate cats, by Calma and Wright, 1944. Cats that have recovered from partial brain removal respond to intravenous acetylcholine by asymmetrical stimulations contralateral to the lesion. This is interpreted as sensitization of the residual parts of the neurones (G. W. Stavraky, 1943). Analogous phenomena result from intramuscular injection of mecholyl in human patients with central lesions (S. M. Fisher and Stavraky, 1944).

Nutritional Functions of Choline.—Choline is a growth factor concerned especially with the transport and deposition of fat and more indirectly with carbohydrate metabolism It is probably used in the formation of choline-phospholipids; it is a source of methyl in the synthesis of other metabolites, interrelated with methionine, homocysteine, betaine and creatine (reviews, W. H. Griffith, 1941; C. H. Best, 1941; McHenry and Patterson, 1944). This *lipotropic effect* is probably produced by stimulation of the phospholipid interchange between the liver and other tissues. Administration of choline to white rats and to depancreatized dogs rapidly lowers the *fat content of the livers*, even with diets rich in fat. It inhibits the deposition of fat into liver of rats poisoned by *phosphorus*, and hastens the removal of fat in the recovery period. It is effective in preventing the fatty liver changes of carbon tetrachloride poisoning of rats (H. M. Barrett, Best and Maclean, 1939), which deuterium tracer studies have shown to be due to withdrawal of fat from other tissue depots. Choline protects against phlorhizin fatty liver, but is not very effective against the fatty liver of *starvation*, which is also due to mobilization of tissue fat. Choline administration prevents the deposition of neutral fat, and to a less extent of cholesterol in the liver of animals fed with pure cholesterol. It protects against fatty liver from *thiamine*. It is partly effective against cholesterol, practically ineffective against *biotin*. *Lipocaic* is ineffective against cholesterol, effective against biotin; *inositol* is ineffective against thiamine, effective against cholesterol and biotin (Gavin, Patterson, and McHenry, 1943).

Conversely, *diets low in choline* result in the deposition of a large amount of neutral fats and a small increase of cholesterol esters in the liver (C. H. Best *et al.*, 1932, 1935, 1936). It may be induced in dogs, and prevented by supplementing the deficient diet with choline or dl-methionine (McKibbin *et al.*, 1944). Deuterium tracer studies on rats and mice show that the accumulation of fat in the liver is due to impaired transportation of fatty acids from the liver to the depots. Cystine and thiamine administration increase fatty acid synthesis (Stetten and Salcedo, 1944). Choline-deficient diet induces a unique *hepatic cirrhosis* in rats, especially if the protein income is low and cystine is added (Lowry, Daft *et al.*, 1941). This cirrhosis is different from any seen in man (R. D. Lillie, Ashburn *et al.*, 1942).

The lipotropic action of choline is probably due to its transformation into phospholipids of the lecithin type, which are a link in the transport of fat. This requires a *molecular structure* of the general configuration of choline and not merely the labile methyl group, but permits certain substitutions, tabulated by McHenry and Patterson, 1944, page 152. Arsenocholine also has marked lipotropic action (A. D. Welch and Landau, 1942). *Methionine* is lipotropic indirectly by supplying *labile methyl* group, for the synthesis of choline and creatine. Choline in turn may be used for the methylation of homocystine to methionine (Du Vigneau, Cohn *et al.*, 1941).

Dietary deficiency of choline or other substances with labile methyl groups produces in young rats, hemorrhagic degeneration of the kidney (W. H. Griffith and Wade, 1939), starting with congestion of the glomerular capillaries, followed by necrosis and calcifications of the cortical tubules (K. Christensen, 1942). *Other visceral changes* of choline deficiency include involution of the thymus; transformation of the lymph nodes in hemonodes; in severe cases, intra-ocular hemorrhage (Griffith and Mulford, 1941); perosis and growth failure in chicks and turkeys (Jukes and Welch, 1942). Addition of choline, methionine or homocystine to the diet of young rats counteracts the inhibition of growth from pyridine, detoxicating this by methylation (Stekol and Conway, 1941). More choline is required in diets rich in protein, especially cystine (Griffith and Wade, 1939).

On the other hand, *excessive administration of acetylcholine* also results gradually in focal necrosis of the myocardium, lungs and kidneys ascribed to ischemia from arteriolar spasm and elastic hyperplasia of the intima (Henlein, 1939).

Continued oral or hypodermic administration of large doses of choline or its esters for several months produces hyperchromic anemia, and multiple hemorrhages and neurone changes in the gray substance of the central nervous system. Administration of folic acid or of liver extract produces remission, with reticulocyte response, even if the choline is continued. Both remedial agents increase serum choline esterase (also in pernicious anemia). This may be a factor in their therapeutic action (J. E. Davis, 1946; Davis and Fletcher, 1946).

Choline administration retards the *deposition of cholesterol* in the liver (Hirnsworth, 1938). It does not, however, promote the regression of *atherosclerosis* induced by feeding cholesterol (A. Steiner, 1938). In *polycythemia*, induced in dogs by exposure to rarefied air, oral administration of choline tends to depress hematopoiesis and to return the cell count to normal (J. E. Davis, 1939). Long-continued excessive feeding of choline chloride produces hyperchromic anemia, amenable to liver extract or dried stomach (J. E. Davis, 1944), but the same dosage failed to have this effect in man (Cartwright and Wintrobe, 1945). In rats it lowers the growth rate (H. C. Hodge, 1945). It produces hyperchromic anemia in dogs (J. E. Davis, 1946). *Thermic shivering* of cooled dogs is temporarily suppressed by injecting acetylcholine, even after atropine (Tournade *et al.*, 1939). The *oxygen uptake* of fresh slices of liver or kidney of rats is increased by choline (Trowell, 1935). Werner and Lichtenberg, 1906, claim that choline injections in rabbits produce sterility or lessened *fertility* analogous to the effects of x-ray or thorium X. Werner and Asher, 1912, found similar blood and skin changes. Prolonged administration of acetylcholine is reported to cause *cancer* in mice, rats, dogs, guinea pigs and fowl (G. E. Hall and Franks, 1938).

***Methacholine Chloride,** U.S.P., *Mecholyl Chloride;* acetyl-β-methylcholine chloride. Very soluble in water. Dose, hypodermically (never intravenously!), 10 mg., increased cautiously to 25 mg.; oral dose, 0.05 to 0.5 Gm.; two or three times daily in water or milk. It is used especially for ion transfer. *Methacholine Chloride Capsules,* U.S.P., usual size, 0.2 Gm. *Methacholine Chloride Injection,* U.S.P., aqueous; usual size, 10 mg. in 1 cc. *Mecholyl Bromide,* N.N.R., is less hygroscopic and is convenient for oral use as tablets, 0.2 Gm., one to three tablets two or three times daily.

Carbachol, U.S.P. (Carbamylcholine Chloride, *Doryl*), is very soluble in water (1:1). Average dose, oral, 3 mg.; hypodermic, 0.25 mg. *Carbachol Injection,* U.S.P., available as 0.25 mg. in 1 cc. *Carbachol Tablets,* U.S.P., available as 2 mg.

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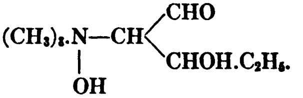
MUSCARINE

Muscarine, an organic ammonium base found in the poisonous fly mushroom (but not in most other poisonous fungi), and a similar base prepared synthetically from choline, produce typical peripheral stimulation of the parasympathetic system and also a nicotine and a curare action. The most characteristic effect of muscarine is a vagus standstill of the frog heart.

Constitution.—Muscarine was isolated by Schmiedeberg and Koppe, 1869, from the fly agaric, Amanita muscaria. Harmson, 1903, obtained 0.016 per cent from the fresh fungus. It is a substituted ammonium base related to choline. Its constitution was established by Kögl, Duisberg and Erxleben, 1931, as



$$(CH_3)_3.\underset{\displaystyle\overset{|}{OH}}{N}—CH\begin{cases}CHO\\CHOH.C_2H_5.\end{cases}$$

Schmiedeberg and Harnack, 1876, who had set up an erroneous formula for muscarine, obtained a compound by the supposed oxidation of choline which they thought identical with natural muscarine, but Boehm, 1885, showed differences in physiological action, and it was then called "*synthetic muscarine*" or "*pseudomuscarine.*" Ewins, 1914, showed that this is not an oxidation product, but a nitrous ester of choline. Its physiologic properties were further studied by Dale, 1914. They agree qualitatively with those of natural muscarine, but exhibit quantitative differences. Weinhagen, 1920, found that slight and accidental variations in the method of its preparation cause differences in the composition of synthetic muscarine.

Muscarine Action on Frog's Heart.—Muscarine causes slowing, with diminished systolic and increased diastolic excursions, and finally *stoppage in diastole.* These effects resemble those of electric vagus stimulation (also the electrocardiogram; Samojloff, 1913); and the results of submaximal vagus stimulation and muscarine are strictly additive, in frogs (O. Loewi), in turtles (Fleischhauer, 1912), and in mammals (Schott, 1911). Muscarine also produces additive results with pilocarpine. Large doses of both paralyze the vagus (Loewi) and the ganglia (Schott). The muscarine effect is more persistent than electric vagus stimulation, and occurs even in calcium-poor hearts, in which ordinary vagus stimulation is ineffective (Loewi, 1912). The refractory period of the heart to artificial stimulation is shortened by weak muscarine, as by vagus stimulation (Raaflaub, 1914). The effect of muscarine on the electric response of the heart was investigated by Mines, 1914. *Perfusion* of the excised frog heart with very dilute muscarine in Ringer's solution produces simultaneous weakening and slowing. If it is perfused in blood, it may also slow without weakening; while perfusion of muscarine blood through the isolated ventricle may give weakening without slowing (Raaflaub, 1914). In *turtle heart,* muscarine increases the auricular tonus waves (Gruber and Markel, 1918). Muscarine causes acceleration of the *crab's heart,* although a well defined inhibitory mechanism exists in these animals.

Location of Action.—In mammalian hearts, muscarine causes no inhibition if the auriculoventricular bundle is cut (Cullis and Tribe, 1913), or in ventricular strips (Leetham, 1913); but in frogs, the muscarine standstill occurs also in the isolated apex, showing that the stimulation is peripheral to the ganglia; and since it can be abolished by atropine (Schmiedeberg and Koppe), the action can not be on the muscle. It is therefore assumed that it stimulates those endings which atropine paralyzes. If muscarine and atropine are exhibited at the same time or successively, their respective quantities determine which predominates, but atropine is much the stronger. The heart may be started by substances which stimulate its muscle directly, *e. g.*, physostigmine, veratrine, digitaline, aniline, camphor, guanidine. The type of contractions under muscarine differs in some respects from those of vagus stimulation (Rhodius and Straub, 1905). In guinea pigs it may cause *bronchial spasm,* similar to that of anaphylactic shock (Modrakowski, 1912). It has no effect on lacteal secretion (Ott and Scott, 1912).

Excretion.—In toads, this occurs quantitatively by the urine (Fuehner, 1908 and 1909).

Central Actions.—Muscarine is reported to cause acute excitement and violent delirium. The fly agaric is said to be used in Siberia as an intoxicant, with effects similar to those of cannabis.

Muscaria poisoning differs from that by other poisonous mushrooms in its relatively rapid course, which is run in one to three hours, and by the phenomena of parasympathetic stimulation. The mortality is not high. *Treatment* consists in gastric lavage, saline purge and atropine.

MUSHROOM POISONING

Many fungi contain poisonous constituents, varying in the different species. Ford, 1913, found that the principles toxic to man belong mainly to three classes: (1) muscarine, which is confined practically to the fly mushroom, Amanita muscaria; (2) substances producing degenerative changes in internal organs (especially Amanita phalloides); (3) substances producing gastro-enteritis.

The toxic effects of *Amanita phalloides* are due entirely to phalloidin, which was isolated as crystals by Lynen and Wieland, 1937. Marked resistance to this can be induced by immunologic technic (M. Vogt, 1938). The several actions were formerly attributed to distinct constituents. Rabe, 1911, claimed to have isolated an alkaloid with muscarine actions. Glucosidal hemolysins were reported in several related varieties, especially in Helvella esculenta (Ford, 1913). They are easily decomposed by heat and digestion and are therefore not concerned in poisonous effects. *Agglutinins*, perhaps glucosidal, are also widely distributed; some of these are not destroyed by boiling, but they are probably not pathogenic (Ford and Rockwood, 1913). Practically all species of Amanita slow or stop the frog heart on direct application. In A. phalloides, this is not due to muscarine, but to inorganic salts (Ford and Brush, 1914).

Poisoning by Amanita phalloides is said to be the cause of ninety per cent of the mushroom deaths in the United States. The *symptoms* set in after a latent period of six to fifteen hours, with sudden abdominal pain, vomiting and diarrhea, stools containing blood and mucus; rapid loss of strength; cyanosis; death in two or three days. The mortality is about 50 per cent; extremely ill patients may recover, or improvement may be followed by fatal relapse. Histologic examination shows extensive necrosis and fatty degeneration of the liver parenchyma, somewhat less of the kidneys. The brain may be edematous (Ford, 1913; Vander Veer and Farley, 1935). Uremia, from greatly impaired kidney function, may be responsible for part of the symptoms (Clark, Marshall and Rowntree, 1915). Dogs and rabbits show marked drop of blood sugar (to 0.028) and decrease of chloride. Rabbits go into hypoglycemia convulsions (Binet and Marek, 1936). The *treatment* comprises evacuation, rest, opiates, liquid diet of high carbohydrate content and intravenous injection of 10 per cent dextrose in 0.9 per cent chloride, 500 to 1000 cc. every six to eight hours.

Phenomena from other poisonous mushrooms vary with the species, but they generally include enteritis and hepatitis. More or less common features are: abdominal pain, nausea, vomiting, violent diarrhea; variable pulse; labored respiration; consciousness unaffected, or delirium; coma or convulsions. Some cause fatty degeneration of the liver and kidneys. Many mushrooms produce abdominal symptoms simply by being indigestible. The *treatment* would be as for phalloides. The chance of poisoning may be somewhat diminished by prolonged boiling, as some of these substances are decomposed in this manner, but reliance on this would be dangerous. Drying does not diminish the toxicity. Verrill, 1914, reported symptoms of inebriation (not dangerous) from eating Panaeolus papilionacens (Maine).

Edible Mushrooms.—The food value of mushrooms is popularly supposed to lie in a large percentage of assimilable nitrogen, but they contain no more than potatoes. As the fiber of mushrooms is also quite indigestible, their dietary value is as a relish rather than as food.

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QUATERNARY AMMONIUM BASES

The organic derivatives of ammonium are strikingly similar in their action. They produce a curare effect, *i. e.*, paralysis of the nerve endings of striped muscle (Brown and Fraser, 1869); some also effect muscular tremors in frogs; and those having three or four methyl groups cause a muscarine effect, *i. e.*, peripheral stimulation of the cardiac vagus; and a nicotine action, *i. e.*, paralysis of sympathetic ganglia. The curare effect evidently depends on 5-valent nitrogen; or rather, on the stereochemic configuration, for the same characteristic is shown by the corresponding phosphorus, arsenic and antimony compounds. The various actions differ in degree with the various derivatives in ways not easily explainable by their constitution (Burn and Dale, 1915).

Tetra-methyl ammonium chloride produces typical curare effect in mammals and frogs. Ammonium convulsions occur in mammals, but not in frogs, being prevented in the latter by the more powerful curare paralysis. The *circulation* shows a fall of blood pressure, generally with slowing of the heart, by peripheral vagus stimulation and peripheral vasomotor depression. The *respiration* is temporarily paralyzed by intravenous injection; in decerebrated animals, this is preceded by respiratory stimulation. The paralysis is due to a curare effect on the phrenic nerves (Marshall, 1913). Loevenhart, 1914, believes, however, that the respiratory action is entirely central; *i. e.*, primary stimulation and later depression of the medullary centers.

Tetra-Ethyl Ammonium Chloride.—In frogs, this produces irregular muscular contractions and tremors; first fibrillary, then tonic. With larger doses, these are succeeded by paralysis. Both actions are seated in the muscle nerve endings. Mammals also show increased excitability and depression of the endings. Burn and Dale, 1915, found no curare or muscarine action, but a good nicotine effect; but Acheson and Pereira, 1946, again confirm a curare effect on the cats' gastrocnemius, as well as blockage of autonomic ganglia, resulting in vasodepression (Acheson and Moe, 1946). It lacks muscarinic and antimuscarinic effects on the nictitating membrane (Acheson and Pereira, 1946). Dilute solutions (1:100,000) improve the working capacity of the heart-lung preparation; high concentrations produce ventricular fibrillation (Acheson and

Moe, 1945). Rabbits exhibit dyspnea, tremors, convulsions and arrest of respiration. In distinction to tetramethyl ammonium, there is no direct action on the circulation; the respiratory effects are also smaller (Marshall, 1914).

Methyl-Ethyl Ammonium Compounds.—The actions of these are, on the whole, intermediate, but without definite ratio to the alkyl radicals (Marshall, 1915; Burn and Dale, 1915).

Furfuryl trimethyl ammonium iodide (*"furmethide"*) acts on parasympathetic stimulant, producing marked sweating, and in larger doses salivation, defecation and vomiting (Fellows and Cunningham, 1944). It is proposed clinically as sudorific, faster and more certain than pilocarpine: 5 mg., hypodermically, cause sweating of the face, arms, thorax and abdomen, usually within two to five minutes. Side actions are rare and insignificant, and are readily controlled by atropine (S. A. Guttman, 1944).

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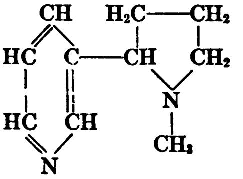
NICOTINE

Nicotine, the chief alkaloid of *tobacco*, has no therapeutic importance, but considerable scientific and toxicologic interest. Both the central and peripheral actions are important; they consist in short stimulation, followed by depression or paralysis. Centrally, small doses cause chiefly a respiratory stimulation; larger doses produce convulsions of the medullary type and arrest of respiration. The action is rapid, approaching that of hydrocyanic acid. Peripherally, nicotine paralyzes all autonomic ganglia, parasympathetic as well as sympathetic. The paralysis may be preceded by stimulation. The most important effects are on the circulatory and gastro-intestinal systems. The intestinal action is complex, and probably involves the muscle directly as well as the ganglia. This probably holds true for its other autonomic effects. Nicotine has several distinct actions on striated muscle, including fibrillary twitchings, curare action and tonus.

Location of Peripheral Autonomic Actions.—The typical paralytic effects of nicotine are exerted on the ganglia, for electric stimulation of the postganglionic fibers remains effective (Langley, 1890). The stimulant effects in many situations are also ganglionic, for they disappear after division of the postganglionic fibers, but persist after degeneration of the preganglionic fibers. The nicotine must therefore act on the "receptive mechanism" of the ganglion cells. These ganglionic effects are overcome by the drugs that act directly upon the receptive or contractile mechanism of the muscle. However, nicotine may also act in part directly on the muscle.

The chief importance of nicotine lies in its habitual use in the form of *tobacco* as an "enjoyment poison" ("Genussgift"), as a stabilizer and lubricator, as "oil on the troubled waters of life." The effects of tobacco are due practically solely to its nicotine. Limited tolerance to the acute toxic effects is soon acquired, after which it acts chiefly as a central sedative. Overindulgence produces chronic nicotine poisoning, with digestive disturbances, functional arrythmias, optic changes, etc. The differences in the various forms of tobacco habit are explainable by differences in absorption.

Nicotine,



a pyrrole derivative of pyridine, is a fluid, volatile, oxygen-free alkaloid, of strongly basic character. It is colorless and almost odorless when freshly prepared, but acquires a characteristic odor and a brown color on standing in the air. Tobacco leaves contain from 0.6 to 6 per cent and up to 15 per cent in some Algerian tobaccos. The natural levo-nicotine is considerably more potent than the dextro. Free nicotine is more potent than its salts because it is more quickly absorbed. Its volatility is not high; the prompt action is due to rapid absorption and high toxicity.

The **central actions of nicotine** consist in stimulation, followed by depression, of the whole cerebrospinal axis, from above downward. The symptoms from large doses resemble those of asphyxia or hydrocyanic acid.

The stimulation may be absent, especially with large doses, so that the animal may drop dead almost instantaneously, without other symptoms. But this is not common. Intermediate doses (in dogs, 1 to 5 mg. per Kg. by vein) produce *nicotine catalepsy* with postural plasticity, autonomic reactions and insensibility to pain (Gutiérrez-Noriega, 1942). The effects of small doses, such as are noticed in smoking, will be discussed under the habitual use. *Direct application to the motor cortex* produces clonus and generalized convulsions, as do caffeine and strophanthin (Rizzolo, 1929). In frogs, the action on the cerebral centers seems to be insignificant, for the effects are the same when the hemispheres are removed.

Medullary Centers.—The respiratory, vagus, vasomotor and emetic centers react strongly, even violently, partly through the carotid sinus and cardio-aortic reflexes.

Spinal Cord.—The motor cells are strongly stimulated, resulting in *convulsions*, with passage of feces and urine. If the nicotine is applied to a part of the cord, the convulsions remain confined to the muscles innervated from this area (difference from strychnine, which acts on the sensory cells). The stimulation is followed by paralysis. The nicotine convulsions are not seated exclusively in the spinal cord, but involve the hindbrain and medulla as well. They are much weakened by anesthesia. The *cutaneous reflexes* of frogs are depressed. Partial tolerance to this action is acquired by repeated administration (Howat, 1916). The *spinal posterior root ganglia* are not affected, even when a 1 per cent solution of nicotine is applied directly to them.

Respiration.—Relatively small doses produce strong but brief stimulation, followed by temporary acapnic inhibition, and with toxic doses by permanent arrest (Winterberg, 1900; de Almeida, 1920). The *hyperpnea* is chiefly reflex from the carotid sinus (Heymans *et al.*, 1931; Anitschkow, 1934) analogous to the hyperpnea of anabasine, lobeline, cyanide and sulfide. The *respiratory arrest* is the usual mode of death in acute nicotine poisoning. Experiments with crossed circulation show that the arrest is due primarily to peripheral (curare) action on the diaphragm and chest muscles (F. E. Franke, 1938). The respiratory center continues to discharge potential impulses through the phrenic nerves after the respiration has ceased, and these are usually increased by further injections of nicotine (H. Gold and Modell, 1936). The asphyxia is rendered more fatal by the preceding convulsions, and if these are prevented by ether, and artificial respiration is administered to give time for the disposal of the nicotine, the animal survives doses that ordinarily cause death (F. E. Franke and Thomas, 1933).

The *bronchial muscle* is constricted in surviving lungs (Baehr and Pick, 1913), but the effects are rather inconstant (Sollmann and Gilbert, 1937). The *ciliary movements of the bronchioles* are arrested by nicotine, but only with relatively high concentrations. In the *frog's esophagus*, they are first accelerated, then slowed and paralyzed, but also require high concentrations. The free alkaloid is about six times more potent than the acetate (Weatherby, 1940). They are markedly slowed by cigarette smoke (Dobrzanski, 1927), but this may involve other ingredients.

Circulation.—The effects of nicotine are complex. They include carotid sinus and cardio-aortic reflexes, direct actions on the vagus and vasomotor centers, stimulation and paralysis of the vagus, stellate, vasomotor and splenic ganglia, increased output of epinephrine and direct effects on the cardiac and vascular muscle. Together they result in initial slowing of the pulse (sometimes to temporary arrest), then acceleration of the heart and rise of blood pressure, which may reach a high peak and may then fall abruptly to shock level. In *smoking*, the effects are complicated by nausea or habituation. They will be discussed under the Habitual Use.

Heart Rate in Mammals.—With small doses of nicotine, the primary slowing is due chiefly to a carotid sinus reflex (Heymans *et al.*, 1931), but with large doses it involves also direct stimulation of the vagus center and of the vagus ganglia.

Arrhythmia.—With larger experimental doses, the slow heart beat is replaced suddenly by great *quickening* through paralysis of the vagus ganglia. The nicotinized heart may be slowed by muscarine, or stimulation of the sinus, but not by stimulation of the vagus trunk. According to Kose, 1904, the secondary acceleration involves ganglionic accelerator stimulation, which passes finally into paralysis. *Electrocardiograms* (dog) often show a nodal rhythm (synchronous action of auricles and ventricles), interrupted by extrasystoles; and other irregularities identical with those of stimulation of the vagi and accelerators, separately or together (Clerc and Pezzi, 1920). *Excised mammalian heart*, perfused with nicotine solution, shows typical vagus effects: first, diastolic standstill; then gradually resumption and finally acceleration above normal, with increased amplitude. The primary standstill is abolished by atropine. The secondary acceleration is probably due to accelerator stimulation (Clerc and Pezzi, 1912.(With *frog heart*, application of nicotine produces brief diastolic standstill (stimulation of vagus ganglia). The heart then resumes its beat and stimulation of the vagus trunk becomes ineffective. The cardiac effects were studied in 1868 by Truhart on intact frogs. Observations of Helt, 1920, on the excised heart by Straub's method show that the effects of increasing doses are (1) Vagus stimulation (diastolic tendency and slowing), spontaneously reversible; arrested by atropine. (2) Disturbance of conduction (partial heart block). (3) Diminished electric irritability. The nicotine is rapidly fixed in the heart and the action becomes irreversible. In *electrocardiographic studies on perfused hearts of frogs and turtles*, Barry (1921) found that the effects vary with conditions: strengthening or weakening; quickening or slowing; dissociation of the chambers; partial or complete arrest; or reversal of the beat (starting in ventricle). With *turtle's auricle*, nicotine, 0.03 to 0.05 per cent, increases the height of the contractions, without changing the tonus or the tonus waves. Concentrations of 0.1 to 1 per cent increase the tonus and the tonus waves; the contraction height may be increased or diminished (Gruber, 1921).

The blood pressure is raised by small doses, exclusively through the carotid body and aorta reflex (C. F. Schmidt and Comroe, 1940). This holds true also for lobeline, cyanide, sulfide, anoxia, CO_2 and alkalis (Heymans *et al.*, 1932). Larger doses stimulate also the vasomotor ganglia (Hoskins and Ransom, 1915). These actions, together with contraction of the spleen, increased epinephrine output (Gley, 1914), and the mechanical effects of the convulsions, drive the blood pressure very high. The nicotine rise is prevented, in cats, by intravenous injection of sodium *sulfathiazole* or of *thiamine*, suggesting transient thiazole blocking of the sympathetic ganglia and adrenal cells (E. P. Pick and Unna, 1946).

The central vasomotor stimulation may persist into death (Pilcher and Sollmann, 1915), but can not make itself felt when the vasomotor ganglia undergo nicotine paralysis. The carotid sinus reflex is then also abolished (Sollmann and Brown, 1912). There may also be direct depression of the arterial muscle. The vessels become dilated and the *pressure falls*. The dilatation can be seen in the intestinal vessels or the rabbit's ear. The vasomotor paralysis is rarely complete, so that direct or reflex stimulation, or a second injection of nicotine, again causes a short constriction. The heart muscle eventually wears out, mainly because of the lowered coronary pressure. Nicotine has no effect on excised *spleen*, but in living animals this contracts strongly, synchronous with the rise of pressure. It is due chiefly to stimulation of the celiac ganglion, and somewhat also to increased output of epinephrine (McCrae, 1930). The *coronary circulation* is slowed by the constriction of the coronary vessels, notwithstanding the raised blood pressure (Morawitz and Zahn, 1914). The *pulmonary and hepatic vessels* are constricted (Berezin, 1914). The outflow from the pulmonary vein is diminished, but the pressure in the pulmonary artery does not rise (W. E. Dixon and Hoyle, 1929). During the nicotine rise of blood pressure the volume of the normal *kidney* diminishes, by arterial vasoconstriction; the volume of a denervated kidney increases passively (Bariéty and Kohler, 1939). The blood pressure of animals in peptone or anaphylactic *shock* reacts but little to epinephrine, but rises sharply under nicotine ($\frac{1}{4}$ mg. per Kg.). This rise, however, is attributed essentially to the increased respiration (J. P. Simonds, 1916).

Peripheral Actions on Frog's Vessels.—By perfusion through decerebrated frogs, nicotine produces immediate vasoconstriction and muscular fibrillation. These effects disappear in a few minutes, during the perfusion, and can not be restored by further nicotine. Epinephrine is still effective. Tyramine suppresses the nicotine constriction almost completely (Handovsky and Pick, 1913).

Cerebrospinal fluid pressure follows the circulatory changes (Dixon and Halliburton, 1914).

The epinephrine output shows a brief increase, followed by marked and enduring decrease, presumably by stimulation and paralysis of ganglia. The epinephrine store of the gland is apparently unchanged (Stewart and Rogoff, 1919). Nicotine also increases the epinephrine output of perfused adrenal gland (Anitschkow, 1927).

The blood sugar level is first raised, then lowered by nicotine. The rise is attributed chiefly to the increased epinephrine output, but in dogs it produces hyperglycemia even after excision of the suprarenal glands (Burstein and Goldenberg, 1928; Hazard and Vaille, 1935). The fall may be due to paralysis of the ganglia or to the lowered blood pressure. Large doses of nicotine prevent the glycosuria which ordinarily follows the injection of caffeine and epinephrine; or on piqûre (Macleod and Dolley, 1905). In guinea pigs the rise may be double the normal level and persist for seventeen days after the last injection (Mosinger *et al.*, 1939).

Tissue oxidation is checked by nicotine. In slices of cerebral tissue the effect is chiefly on lactic and pyruvic acid, much less on dextrose, and practically none on succinic acid; with kidney and testis, dextrose oxidation is inhibited as much as lactic acid is (Z. Baker *et al.*, 1938).

Effects on Glands.—Secretion is generally stimulated through the ganglia. This is particularly prominent with the *saliva*. Small doses, however, change the response to stimulation of the chorda nerve, so that this diminishes secretion (Dale and Laidlaw, 1911). *Lacteal* secretion is not increased by nicotine (Ott and Scott, 1912). Large doses suppress for some hours (Hatcher and Crosby, 1927). A *local sweat response* is produced in man by intracutaneous injection of dilute solutions of drugs of the nicotine group (nicotine, 1:200,000; alpha lobeline, 1:2,000,000; acetylcholine, 1:40,000). It appears to be an axon reflex and is suppressed by adding procaine, 1:100,000 (J. M. Coon and Rothman, 1941).

Oviductal secretions of birds.—Nicotine has no effect on the output of shell material (Riddle and King, 1921).

Digestive Tract.—Nicotine produces nausea, emesis and violent diarrhea. The emetic action is mainly central, the intestinal mainly peripheral.

Nicotine emesis is probably due to medullary stimulation (Eggleston and Hatcher, 1915). It may be evoked by direct application of a minute trace to the medullary emetic center (Hatcher and Weiss, 1923). It is antagonized by atropine (Eggleston, 1916). *Excised stomach* is contracted in most mammals, but relaxed in a few forms (M. Smith, 1918). The effects on *mammalian intestine* are chiefly peripheral, *i. e.*, essentially alike in intact animals and in excised intestine. Small doses stimulate the muscle and slightly increase its tone. Larger doses produce violent stimulation, culminating in intense contracture (Nasse); but this is soon followed by inhibition of the movements and relaxation of the tone (Pohl; Ikeda, 1916). Dogs show relatively more stimulation and less depression. The contracture is abolished by atropine. The ganglia are also paralyzed, so that the responses to stimulation of the vagus or splanchnic are abolished (Mulinos, 1927).

In **urinary bladder** of cats, nicotine produces contraction followed by relaxation. The responses are not affected by section of the nerves or by atropine (Edmunds and Roth, 1920). G. B. Roth, 1917, found practically no effect on *excised ureter*. Macht, 1916, describes primary stimulation and secondary depression. The *retractor penis muscle* is stimulated by nicotine (Edmunds, 1920). As it does not contain any ganglion cells (Fisher), the action is presumably on the receptive mechanism. The effects on the *uterus* are described in the general discussion of autonomic poisons.

The pupils show both contraction and dilatation at different times, nicotine acting upon the ganglia of both the oculomotor and sympathetic fibers. There may even be a direct action upon the iris muscle. The effect is different in different animals: the dog and cat usually show dilatation; the rabbit first constriction and then dilatation.

Skeletal Muscle.—The injection of nicotine into frogs produces fibrillary twitching merging into tonic contracture (O. Kushima, 1919). The minor grades may cease temporarily on section of the nerve, but they return, especially on stimulation. They occur also in excised muscle and after degeneration of the nerve endings, so that they are intramuscular. Microscopic examination shows that the contracture may be confined to the region of the end-plates and that smaller concentrations of the poison ($\frac{1}{500}$) are effective at this region (Langley, 1913, 1914). This holds true also for other muscle poisons, for instance caffeine, and may mean that the sarcolemma is more permeable at this place; but it has been interpreted as evidence that the nicotine acts on a receptive substance assumed to be localized especially about the intramuscular "end-plate." The nicotine stimulation is mutually antagonistic with curare, atropine, cocaine and procaine (Frank and Katz, 1921; Schueller and Athmer, 1921). A number of other poisons produce essentially identical effects: namely, physostigmine, guanidine (Fuehner, 1920; Frank and Stern, 1921), acetylcholine (Riesser and Neuschloss, 1922), barium and probably veratrine. They also show essentially the same antagonisms. Physostigmine, guanidine and barium become ineffective rather early after nerve degeneration, which evidently induces intramuscular degenerations that interfere more with the response to these drugs than with those to nicotine and acetylcholine. As the stimulation by all these drugs is mutually antagonistic with curare, which does not paralyze the muscle to direct stimulation, it may be assumed that they and curare act on a "receptive mechanism" in the striped muscle.

The *muscle of fowls* is especially susceptible to the tonus (Langley, 1906; Edmunds and Roth, 1908).

Mammals also show fibrillar contractions, but of central origin. Excessive doses of nicotine do not produce these central convulsions, although they do not prevent strychnine convulsions (Langley, 1918).

Tobacco Smoking on Ergographic Response.—This produces a periodicity in the contractions, apparently due to central fatigue and depression (Raphael, 1920).

Curare Action.—Nicotine has a curare-like effect, which becomes prominent later. In the milder stages, equally strong or stronger current is required when the stimulus is applied to the nerve than when it is placed on the muscle. In the normal preparation the opposite is the case. The excitability and irritability of the muscle cells are also diminished by nicotine on direct application. The curare action may lead to paralysis of respiration in mammals (Thomas).

Invertebrates.—In the *squid* (Loligo) nicotine acts on the cerebral and not on the stellar ganglion (A. R. Moore, 1919). In *starfish* (Asterias) it produces ventral flexure, whereas strychnine produces dorsal flexure. When both drugs are used, the strychnine effect predominates (Moore, 1920).

Insecticide.—Nicotine is one of the most efficient insecticides, especially for soft-bodied insects, such as plant lice. It is generally sold as a 40 per cent solution of the sulfate, to prevent volatilization. About two million pounds of this solution are used annually in the United States (P. A. Neal *et al.*, 1941). It kills the insects by paralysis, ascending the ventral nerve cord from the abdomen to the brain. It produces structural changes in the nerve cells, analogous to those of oxygen deprivation (McIndoo, 1916). Both optical isomers are equally toxic (Gause and Smaragdova, 1939).

Antiseptic Action.—Tobacco juice and smoke are antiseptic, and Fullerton, 1912, claims that they tend to preserve the teeth. Common experience shows that they are not effective.

Local Actions.—Free nicotine is caustic by its alkalinity. Strong solutions paralyze the nerve fibers.

Fate.—Nicotine is *absorbed* rapidly from mucous membranes and especially from the lungs; more slowly from hypodermic injections. Serious poisoning has occurred from the intact skin (J. M. Faulkner, 1933). Absorption from "chewing" 10 Gm. of tobacco amounted to 5 mg. of nicotine in the first hour (D. Gaede, 1940). It is *excreted* only in small part (4.2 to 12.8 per cent; A. C. Corcoran *et al.*, 1939), mainly by the urine, where it can be demonstrated after smoking, through its catatonic effect on rats (Dingemanse and Freud, 1933), as well as chemically.

The urine of habitual smokers contains 1.4 to 9.8 mg. per twenty-four hours (A. C. Corcoran *et al.*, 1939). It disappears within three or four days after discontinuing the smoking. It appears to be responsible for the pressor effect of many urines (Helmer *et al.*, 1939). Smoking forty cigarettes in a day, 2 to 8 mg. of nicotine are excreted in the urine, representing 2 to 8 per cent of the retained nicotine of the inhaled smoke. The amount recovered in the urine is about doubled if the urine is rendered more acid by administering ammonium chloride, and it is decreased to a fourth by giving alkali, presumably by absorption of free nicotine from the urinary bladder (Haag and Larson, 1942). It is also excreted by the lungs and sweat, a small amount by the milk, 0.12 to 0.5 mg. per liter of milk, when smoking one to twenty cigarettes per day; there was no demonstrable effect on lactation or nurselings (Perlman and Dannenberg, 1942). *The unexcreted nicotine is destroyed,* chiefly in the liver. Rabbit's kidney and lung, as well as liver, contain an enzyme system capable of detoxicating nicotine (E. Werle, 1938). There is no significant increase of nicotinic acid or its derivatives in the urine (Larson and Haag, 1942). Dixon and Lee, 1912, claimed that the destruction is increased by habituation. Biedl *et al.*, 1932, report that the blood pressure is more sensitive to nicotine in dogs whose liver has been removed. With frog's liver, however, Clark, 1912, found no destruction.

Acute Nicotine Poisoning.—Fatal nicotine poisoning occurs from accidental ingestion of nicotine insecticides: 288 cases were reported in the registration area of the United States in the five years of 1930 to 1934 (J. B. Beeman and Hunter, 1937; F. E. Franke and Thomas, 1936). Serious poisoning occurs industrially from inhaled tobacco dust (Burstein, 1927), in nicotine extraction (Genkin *et al.*, 1935) and sometimes through the medicinal use of tobacco, especially by the laity.

The application of tobacco to wounds or bruises is not without danger. E. G. Garvin, 1913, reported the death of a girl of six and one-half years, forty-five minutes after the administration of less than 1.5 Gm. of tobacco by enema, against pinworms.

Toxicity.—Nicotine is one of the most fatal and rapid of poisons; the vapor arising from a glass rod moistened with it and brought near the beak of a small bird causes it to drop dead at once, and two drops placed on the gums of a dog may give a similar result. The fatal dose for a man is about 40 mg. of nicotine, with death in five to thirty minutes. The fatal dose of tobacco is about 2 grams; one cigar contains a quantity of nicotine which would prove fatal to two persons, if directly injected into the circulation.

Symptoms.—In lighter cases, such as occur in *smoking*, the peripheral and nauseant actions predominate. There is first an increased flow of saliva, partly reflexly through the mechanical irritation of smoke, but mainly by direct stimulation of the ganglia through the nicotine. Nausea, vomiting and diarrhea soon appear. There is a sensation of oncoming sweat, which does not actually break out. A feeling of exhaustion appears early, partly as the result of nausea, partly as the first indication of central collapse action. Palpitation is also noted. *Severe cases* show immediate faintness, prostration and muscular weakness; severe nausea, vomiting and diarrhea, followed quickly by collapse with or without convulsions. Death occurs usually within a few minutes after ingestion, but may be delayed for several hours. *Autopsy* often shows hemorrhagic gastritis or acute cardiac dilatation (Beeman and Hunter, 1937). Anemia of the meninges and peculiar changes of the cortical cells have been described in animals.

In man, 1 to 4 mg. of pure nicotine by mouth produced prompt burning in the mouth, a scratching sensation in the pharynx, increased salivation, a sensation of heat spreading from the region of the stomach over the whole body; excitement with headache appeared, then vertigo, confusion, disturbed vision and hearing, photophobia, dryness in the mouth, cold extremities, nausea, vomiting and diarrhea. Respiration quickened, but difficult. Pulse at first increased, then irregular. After forty-five minutes there was syncope, with clonic spasms. Recovery occurred, but general depression persisted for three days. With *intravenous injection* of 1.5 to 6 mg. of nicotine, Maddock and Collier, 1933, observed increase of respiration, cutaneous vasoconstriction, rise of systolic pressure by 12 to 16 mm., and increase of heart rate by 8 to 36 beats, without any seriously toxic phenomena.

Subacute industrial nicotine poisoning as observed in nicotine extraction occurs usually as acute outbreaks with predominance of parasympathetic stimulation: bradycardia (the most frequent symptom), arrhythmia, hyperchlorhydria, smooth muscle spasticity, salivation, sweating. Sympathetic stimulation was indicated by angiospasm and tremors. The pupillary reactions were disturbed (Genkin *et al.*, 1935).

Proof of Nicotine Poisoning.—The odor furnishes valuable evidence. The extracted nicotine may be tested on animals. The muscular tremors and the positions which a frog assumes after nicotine (Van Praag, 1854) are characteristic, especially the folding of the hindlegs on the back. A control animal should be observed. Nicotine is very *resistant to putrefaction* and has been isolated from the decomposed bodies of animals three months after death.

Treatment of Acute Nicotine Poisoning.—If the stomach has not been thoroughly evacuated by vomiting, it should be washed. Charcoal or permanganate should be administered. *Artificial respiration is the most important measure.* It should be instituted as soon as collapse appears, and prolonged until the peripheral muscular action of nicotine has worn off. Epinephrine may be injected if the heart has failed (Franke and Thomas, 1936).

Injections of formaldehyde and *methenamine derivatives*, especially iodomethylate of tetramethylene tetramine, effectively antagonize many of the nicotine actions, including the toxic effects on the heart, blood pressure and respiration, and on the isolated intestines (J. Gautrelet and Halpern, 1934; Corteggiani, 1935). Their clinical usefulness requires confirmation.

Related Alkaloids.—Several plants contain alkaloids closely related to nicotine and having similar actions:

Nicotiana sylvestris contains *nornicotine*, lacking the methyl group of nicotine. It has similar actions, but is less potent (P. S. Larson *et al.*, 1945). *Duboisia hopwoodii*, chewed by the natives of Australia, contains as its chief alkaloid *piturine*, which is *d-nornicotine*. Its actions are qualitatively identical with those of nicotine (C. E. Hicks *et al.*, 1935).

Anabasine, an isomer of nicotine, occurring in a weed of the pigweed family, perennial in northern Africa, Russia and Armenia, is identical with the synthetic *neonicotine*. Like nicotine, it first stimulates and then depresses autonomic ganglia, its potency being one-fifth to one-third that of nicotine. It also exerts the other actions of nicotine; for instance, on the respiration (H. B Haag, 1933; Anitschkow, 1935). As *insecticide*, it is cheaper than nicotine and more effective against aphides, but less effective against other insects.

Cytisine, an alkaloid of the ornamental Laburnum tree, resembles nicotine in its actions (Dale and Laidlaw, 1912), stimulating and then paralyzing autonomic ganglia, the sympathetic being more susceptible to it than to nicotine (Zachowski, 1938).

Caulophyllum contains methyl-cytisine, with similar actions; also volatile oil, a saponin (Lloyd's Leontin), and caulophyllosaponin (Power and Salway, 1913).

Pyridine, C_5H_5N, one of the nuclei of nicotine, is a strong local irritant with low toxicity; a 10 per cent solution has been used by atomizer in asthma and fetid bronchitis. It produces first dyspneic then shallow respiration. Brunton and Tunnicliffe (J. Physiol., *17:* 292) refer the effects mainly to sensory paralysis. Large doses arrest the heart. Smaller amounts stimulate the bone marrow to increased production of blood platelets (R. L. Lee and Minot, 1917). Its toxicity for man and animals was studied by L. J. Pollock *et al.*, 1943. *The inhalation of crude pyridine vapor* by cats, an hour daily for three to four months, resulted in pulmonary emphysema and chronic bronchitis and slight fatty infiltration of the liver and kidneys (H. Ludwig, 1936). *Derivatives of pyridine* were studied by de Caro, 1927, for relation of structure to muscle-nerve action.

Pyrrole, $(HC_2)_4NH$, the other nucleus of nicotine, has a low local and systemic toxicity. Its action and those of its alkyl ketones on frogs were studied by Rabbeno, 1929 and 1930. They cause tonic contraction of excised gastrocnemius muscle, passing into rigor and not affected by atropine or physostigmine. In mammals, pyrrole and its derivatives, pyrrolidine and pyrrolidone, give a *melanotic color* to the urine, and pyrrolidone produces temporary darkening of the fur of rabbits, disappearing again as excretion progresses (Sarcadi, 1922). *Intraperitoneal injection* of pyrrole into dogs results in epileptic seizures, with succession of aura and tonic and clonic convulsions, at first with lucid intervals between attacks. Death occurs by status epilepticus. These effects occur only if the pyrrole is absorbed by the portal system and are ascribed to liver injury. The brain shows pathologic changes (Rezek, 1937).

TOBACCO AS A HABIT-DRUG

Tobacco is smoked, chewed, snuffed, or rubbed on the gums ("dipped") for its tranquillizing and stabilizing effect on the psychic and emotional functions. The effects are due practically entirely to the nicotine. Tobacco smoke contains other toxic constituents, but their quantity is too small to be practically important. This has been proved both by chemical considerations and by animal experiments (Lee, 1908; K. B. Lehmann; van Leeuwen, 1918). In the habitual use of tobacco, a limited tolerance is acquired against the acute nauseant and emetic effects of nicotine, but it is confined to the quantity to which the individual is accustomed and does not extend to most of the other actions, nor to the total toxicity. When the tolerance has been acquired, the continued use of tobacco within the individual limit of tolerance does not cause unpleasant symptoms; but if the limit is exceeded, acute or chronic phenomena arise. They take many forms: especially local irritation of the respiratory tract; digestive and nutritional disturbances; functional cardiac arrhythmias; depression of various parts of the central nervous system; neuralgias; more rarely impairment of vision. Exceptionally, these may occur after a long period, some twenty years, of moderate use. When the habitual use has become firmly established, withdrawal or even limitation of the usual allowance, causes craving, discomfort and restlessness, as with other drug habits, but not as severe as with morphine. They are probably purely psychical, the absence of an accustomed emotional crutch, and pass their acme in about three days.

Historical.—Tobacco (Tábacum), the dried leaves of Nicotiana Tabacum, an herby plant belonging to the potato family, was probably indigenous to tropical America. It was smoked by the natives at the time of Columbus and was introduced into Spain and Portugal in 1559, and from there to France and Italy; into England in 1585, directly from America. Its use was at first combated by Church and State as an enslaving addiction. The opposition ceased when Richelieu in France and Charles I in England discovered its possibilities as a source of taxation (H. Beer, 1931). Tobacco was first cultivated by white men in Virginia in 1612; fifteen years later, 500,000 pounds of cultivated tobacco were shipped annually to England.

The *consumption of tobacco* increases considerably in periods of national restlessness and exhaustion. Before World War I, the annual world production was estimated as one and a half million tons; by 1920 it had increased to two and a half millions, and by 1929 perhaps three and three-fourths millions (Conte Corti). The consumption of cigarettes in the United States increased from eight and a half millions in 1910 to 190 trillions in 1941.

Tolerance and Habituation.—The quantitative effects of nicotine vary considerably in different persons. Similar variations are observable in animals. Children and adolescents appear more susceptible than adults, but there are no critical data for comparable conditions. The rapidity and completeness of the habituation also vary with individuals, depending partly on individual susceptibility, partly on the manner in which the drug is used, whether the smoke is inhaled, the saliva expectorated, and the like.

Wahl, 1920, found that nonhabituated men are nauseated by 1 or 2 mg. of nicotine, by mouth; tobacco users required more than 8 mg.

Habituation in Animals.—Edmunds, 1909, and others could not produce tolerance. Behrend and Thienes, 1933, also found that adult rats did not become tolerant, but young rats developed definite tolerance to minimal convulsive doses and to the conditioned salivation reflex, but not to minimal fatal doses. Hatcher, 1904, showed that the serum of habituated animals does not protect others against intoxication. Dixon and Lee, 1912, claimed that the liver of habituated animals destroys nicotine somewhat more rapidly. Edmunds, 1916, failed to confirm this.

Psychic Effects.—Habitual users of tobacco experience a certain pleasure, which appears to resolve itself into a reposeful, calming and stabilizing effect on their nervous equilibrium, provided that the quantity of the tobacco is not excessive; otherwise it may increase nervous excitability. *The stabilizing action* has been demonstrated objectively by the threshold to painful electric stimuli. Smoking leaves the normal threshold unaffected, but both excessive and defective irritability are brought toward normal, the effect being similar to that of rest (Mendenhall, 1925). In the same sense, smoking tends to nullify the sensory depression by analgesics and hypnotics (Hale and Grabfield, 1923).

Monkeys also "smoke tobacco with pleasure," and "have a strong taste for tea, coffee and spirituous liquors" (Charles Darwin, "Descent of Man," Chap. I).

The nicotine is not the only element in the enjoyment and tranquilization: the esthetic satisfaction of the aroma of the tobacco, the haze of the smoke and the reflexes from the mucous membrane of the mouth and nose also play a part. But a group of subjects, after becoming accustomed to hypodermic injection of 1.2 to 6 mg. of nicotine, preferred this to the smoking of a cigarette. They also obtained similar psychic effects from 4 mg. by mouth or 0.1 mg. by vein (L. M. Johnston, 1944). Habitual smokers obtain less satisfaction from cigarettes of low nicotine content (0.34 mg.) than from the same cigarettes enriched with nicotine to 1.96 mg. (J. K. Finnegan *et al.*, 1945).

Haggard and Greenburg, 1934, suggested that nicotine tranquilizes by restoring the *blood sugar level* in fasting; but this can not be significant, as the effect is the same after meals, when it does not raise the sugar level (D. L. Thomson, 1934).

The resultant of these actions on *efficiency* depends greatly on individual conditions, on temperament, fatigue, difficulty of the tasks, suggestion, etc., so that direct tests of efficiency have given discordant results. For instance, the speed and accuracy of arithmetic addition have been reported as increased (Berry, 1917), and as unaltered (Wahl, 1920). The sensation of fatigue and discomfort (including hunger) can be temporarily obscured, and a temporary extra spurt of effort secured; but whether the total performance is increased is an open question. Deprivation of tobacco induces in habitual users a condition of nervousness, analogous to the craving of the more serious drug habits, that interferes with work, especially with mental effort and concentration. Attempts have been made to evaluate the effects of tobacco by comparing the efficiency of groups of smokers and nonsmokers. Such studies generally show some superiority of the nonsmokers; for instance, in the endurance of telegraph workers (Baumberger and Martin, 1921); scholarship (E. L. Clark, 1900; Meylan, 1910); growth in youth (Seaver, 1897); resistance to tuberculosis (Flick, 1908). It has not been possible, however, to decide whether the apparent inferiority is the effect or the cause of the tobacco habit: those who are handicapped by inferiority naturally feel the greatest need for, and succumb most readily to, the euphoria of smoking.

Effect on *Muscular Work.*—Baumberger *et al.*, 1921, found that habitual smoking (outside of working hours) did not appear to affect the work output of glassblowers, who require strenuous physical dexterity. Chewing during the work appeared to impair the output (perhaps by a slight curare action?). With the ergograph, Palmen, 1911, found that cigarette smoke at first increased the *muscular work*, but that fatigue set in sooner and the total activity was decreased.

Local Effects.—The nicotine and other basic constituents of the smoke act as fairly strong irritants, as shown by the biting sensation on the tongue, noted especially when the smoke is concentrated on one point, as in pipe smoking, and by the watering of the *eyes* when they are touched by the smoke. The constant irritation of the mucous membrane of the mouth, throat and pharynx leads to *catarrh* and hoarseness. The tar of cigarette smoke is chiefly responsible for these effects (W. D. McNally, 1932). Cigarette smoke also depresses the effectiveness of the tracheal *cilia*, averaging 40 per cent. This is not proportional to the nicotine content and is especially marked with mentholated cigarettes (W. L. Mendenhall and Shreeve, 1937, 1940). Appleton and Lehmer, 1928, reported that cigarette smoking diminishes the *mouth bacteria*, but the decrease is temporary and not impressive.

Long-continued irritation by carcinogenic constituents of the tar (Roffo, 1939) appears to favor development of *epithelioma* of the lip and tongue, if the quantity consumed is large or the smoker specially disposed.

Chewing of tobacco also appears to be an etiologic factor in oral cancer, starting with leukoplakic changes of the cheek where the cud is held (Friedell and Rosenthal, 1941). Tobacco tar produces papillomas when painted daily for three months on the skin of rabbits. This is exceptional with tar of denicotinized tobacco (C. M. Flory, 1941). Nicotine as such is not concerned in tumor production in rabbits (A. H. Roffo, 1941).

Acute Circulatory Effects of Smoking Tobacco.—*In unhabituated individuals*, or when the customary amount is exceeded, there is a brief and moderate rise of blood pressure, succeeded by considerable fall when the nausea-collapse sets in. The pulse rate quickens as much as 20 per minute. The cardiac output is considerably increased (Grollman, 1930). *Experienced smokers*, when they remain within their customary limits, show no demonstrable change in blood pressure (or slight rise, Lee, 1908), or cardiac output, and slight or no increase of pulse rate (Grollman, 1930). Lowering and inversion of the T wave of the electrocardiogram occur after smoking in about a third of the subjects (Graybill *et al.*, 1938). It is commonly believed that excessive smoking causes "shortness of breath," but the concept is indefinite and difficult to establish.

Definite and prompt *cutaneous vasoconstriction* can be demonstrated, in experienced as well as inexperienced smokers, by lowering of the skin temperature (Maddock and Coller, 1933), and by microscopic observation of the nailfold (I. S. Wright and Moffet, 1934).

It occurs even with a single cigarette, is more pronounced with inhalation of the smoke and lasts half an hour after the smoking. The vascular response to smoking is generally parallel to the response to cold (E. A. Hines and Roth, 1938). It is most pronounced in healthy young adults (Cates and Giovanaszzi, 1939). It is confined largely to the skin, so that the blood flow through the arm is not decreased (Abramson). It is due chiefly to the deeper inspirations and occurs also with denicotinized or cornsilk cigarettes, or with puffing an unlighted cigarette (Mulinos and Schulman, 1940; F. E. Franke and Hertzman, 1940; W. F. Evans and Stewart, 1943). However, G. M. Roth *et al.*, 1944, claim that all the circulatory effects of smoking two cigarettes, by habitual smokers, are duplicated by intravenous injection of 2 mg. of nicotine and not by smoking cornsilk cigarettes.

J. Parkinson, 1917, studied the immediate circulatory response to the smoke of four or five cigarettes in normal subjects and those with "*soldier's heart.*" All the subjects who "inhaled" the smoke showed effects, which were generally greater in the patients with circulatory instability. The response consisted in increased pulse rate, averaging nine beats in the patients, and slight rise of blood pressure, 5 to 10 mm., systolic, 5 mm. diastolic. Respiration was unaffected, but exertion easily rendered the subjects "breathless." W. G. Thompson and Sheldon, 1917, investigated the acute effects of smoking in *patients with high blood pressure.* The response differed greatly: the maximum effects ranged from a rise in systolic pressure of 25 mm. and in pulse pressure of 22 mm. to a fall in systolic pressure of 30 mm. and in pulse pressure of 34 mm. Rise, fall and no effect were about equally numerous, and varied even in the same patient. There was no difference between cigars and cigarettes. Nicolai and Staehelin, 1910, found that in tobacco users the heart rate averaged somewhat higher, especially in work; no definite changes could be made out in the systolic and diastolic blood pressure or electrocardiograms.

In *animals* the effect of tobacco smoke on the circulation is identical with that of nicotine, showing that this is indeed the active agent.

In *intact mammals*, there is a brief fall, then a high rise of blood pressure. The heart is slowed, then quickened. Cardiac disturbances appear, especially auricular fibrillation, and these are antagonized by formaldehyde compounds, as is nicotine (Hendrikson, 1930; Tournade and Malmejac, 1930; J. F. Johnson and Winder, 1942.) The electrocardiographic changes are the same as with nicotine (Mattioli, 1932). *Perfusion of excised heart* (rabbit's) with Ringer's solution through which tobacco smoke had been passed produced the typical nicotine effects on perfusions through excised rabbit's heart, *i. e.*, temporary vagus standstill. Prolonged perfusion, however, leads to permanent arrest, due not to the nicotine, but to collidine and other bases that occur in the smoke of tobacco or other leaves, for instance, oak (Clerc and Pezzi, 1914). In *heart-lung preparations* (dog) tobacco smoke produced complete nicotine paralysis of the vagus. The rhythm of the denervated heart was not changed. The *coronary vessels* were dilated both by smoke and by nicotine. Direct effects on the myocardium occurred only with amounts far above those of ordinary smoking (Mansfield and Hecht, 1933).

Delayed functional cardiac disturbances are common. The first warning symptoms are occasional palpitation, quickened heart rate and functional arrhythmia. These become persistent if the nicotine is continued, but disappear on withdrawal. In advanced cases, the abstinence must be continued for months. The arrhythmia is due to extrasystoles, pointing to increased irritability of the cardiac structures. The extrasystoles are usually auricular. Auricular fibrillation and "flutter," and sino-auricular block have been encountered (Neuhof, 1916). The block disappeared within three days after stopping the tobacco. In graver cases, the cardiac irregularity may lead to sudden fainting (*syncope*). *Respiratory distress* accompanies the marked cardiac phenomena.

Functional extrasystoles occur also after coffee, digitalis, quinidine, salicylates and in acute infections and neurasthenia. They are less frequent when the heart rate is above 120, and may therefore be suppressed by exercise and fever (M. Campbell, 1929).

The cardiac disturbances may cause precardial pain and hyperesthesia, which may radiate to the left nipple and ulnar surface of the left arm. Nicotine has little if any causative relation to *angina pectoris*, for all statistical studies confirm that the proportion of heavy, light and moderate smokers is not materially different for patients who develop angina, and for a comparable group of the general population. But a developed angina may be exaggerated by smoking (just as ordinary physical exercise does not produce angina, but in angina the exercise provokes the attack). Patients with developed angina, therefore, tend to smoke less because they are afraid of nicotine (P. D. White and Sharber, 1934).

Coronary ligation in animals renders the heart hypersusceptible to nicotine electrocardiogram disturbance. The exaggerated response diminishes with time (Bellet Kershbaum *et al.*, 1941).

The question as to *arteriosclerosis* is not clear. Statistics indicate that patients with *thrombo-angiitis obliterans* are nearly always heavy smokers (B. Weicker, 1940). The incidence of arteriosclerosis obliterans in diabetes mellitus is nearly twice as great in smokers as in nonsmokers. The statistics show no significant difference between light and heavy smokers (Weinroth and Herzstein, 1946). When the vessels are diseased, as in endarteritis obliterans and in coronary disease, the acute vasoconstrictor action of nicotine would tend to interfere with the collateral supply (Maddock, Malcolm and Coller, 1936).

In rabbits, chronic nicotine poisoning produces anatomic arterial and cardiac changes, similar to those of epinephrine (Adler, 1914). Lissauer, 1914, also described histologic changes in the cardiac and other ganglion cells. It may be doubted whether these results should be transferred to man.

Experimental Endarteritis.—M. Friedlander, Silbert and Laskey, 1936, report the production of arterial changes by injection of tobacco into male rats, while female rats failed to develop them. Other investigators have been generally unsuccessful in producing vascular damage in rats or rabbits, even when convulsant doses of nicotine were injected twice daily for two to six months (Thienes, Behrendt *et al.*, 1937).

Acute Effects of Smoking on the Gastro-Intestinal Tract.—In those who are not accustomed to tobacco, or who exceed their accustomed quantity, it produces the nausea, emesis and diarrhea discussed under nicotine. With experienced users, the smoking of one to three cigarettes, or hypodermic injection of 0.4 mg. of nicotine, generally causes some increase of saliva (reflexly), and depression or inhibition of the hunger contractions (Carlson and Lewis, 1914), also reflexly; but significant gastric retention or increase of gastric acidity is exceptional. The motility of the colon is generally increased. There is little if any effect on the secretion of gastric juice and bile. If the tolerated dose is exceeded, undesirable effects set in, and patients with gastric ulcer and colon disturbances should be cautioned against excess (Schnedorf and Ivy, 1939). *Intestinal motility* is increased by cigar or cigarette smoke, both in those accustomed and in those who are not. The effect begins in a few minutes and lasts for half an hour to an hour after the smoking is stopped (Simici and Popesco, 1936). H. Rosenblum, 1938, reports that a single cigarette may increase the volume and acidity of gastric juice, especially with gastric ulcer patients.

Chronic Digestive and Nutritional Disturbances.—Various forms of "nervous dyspepsia" develop fairly early with continued excessive smoking. They include loss of appetite, hyperchlorhydria, alternating constipation and diarrhea, loss of weight and anemia. They are due partly to the local irritation of nicotine and tar, partly to degenerative cellular changes and partly to the nervous irritability.

Ingestion of tobacco tar by rats in nontoxic dose for periods up to two years produced gastric lesions in half of the animals. They involved especially the glandular zone, beginning with hemorrhagic ulceration, progressing to rodent ulcer, and after a year to carcinoma (Roffo, 1941).

A direct action upon *hematopoiesis* may have a part in the anemia, the continued administration of nicotine to animals leading to diminution of red corpuscles, and increase of leukocytes. It is also claimed that it diminishes the oxygenating power of hemoglobin.

Salivary Glands.—The amylolytic activity of the saliva may be completely lost, with histologic changes in the glands. They may recover in time, after withdrawal (Bosco, 1930).

Metabolism.—Changes of basal metabolic rate on smoking are inconstant, small, and in both directions (Goddard and Voss, 1942). There are no significant effects on the respiratory quotient, nor on the blood sugar (see below) or blood lactic acid (A. B. Dill *et al.*, 1934). With habitual smoking, the nitrogen excretion may be rather more diminished than the assimilation, so that there may be a gain in body nitrogen. Transitory albuminuria may occur. The *organ weights* of rats do not show significant changes on nicotine feeding, if they are compared with controls of equally restricted food income; nor do the viscera show histological changes (R. H. Wilson *et al.*, 1938).

Blood Sugar Level.—Smoking has little effect on the normal level, but raises the fasting level (0.08 to 0.1 per cent) to normal (0.12 to 0.14 per cent), and the fasting respiratory quotient from 78–82 to 85–90, presumably by increasing the epinephrine output. It returns to the fasting level in about half an hour (H. W. Haggard and Greenburg, 1934; Burstein and Goldenberg, 1928). The rise of the blood sugar is more marked in *diabetic patients*, amounting to 0.4 to 0.5 per cent (Caponnetto, 1928).

Nervous Disturbances.—Excessive use of tobacco may induce headache, insomnia, anxiety, irritability of temper, tremors, heightened reflexes, neuralgias, vertigo, sometime mental slowness and lethargy.

Other effects which have been attributed to nicotine but with insufficient cause are: impotence, epilepsy and insanity (G. W. Jacoby, 1898; Naecke, 1909).

Nicotine blindness is rare. It seems to be favored by alcoholism. This, and the associated thiamine deficiency, may be the real cause. The sight gradually becomes dim, with central scotoma, impaired accommodation and often miosis. It is always bilateral. The anatomic changes consist in retrobulbar optic neuritis, with subsequent atrophy. Until degeneration has set in, a complete cure can usually be effected by abstaining from nicotine; later, this will only arrest the further progress (de Schweinitz, 1896). The amblyopia has been attributed to vasoconstriction. Vasodilators (sodium nitrite, acetylcholine) are reported to hasten the recovery of vision (Pfimlin, 1930; W. F. Duggan, 1935, 1937).

Other Toxic Amblyopias.—Many poisons may produce blindness, temporary or permanent, in susceptible individuals, especially on continued administration. This has been recorded for stramonium, cannabis, chloroform, opiates, carbon disulfide, arsenic, lead, iodoform, aspidium, quinine, salicyl, methyl alcohol, and the like. For most of these the changes are analogous to those of nicotine. With methyl alcohol, quinine and salicyl, the retinal ganglion cells are also involved. The metals and aspidium may produce primary optic atrophy without preceding neuritis (de Schweinitz, 1896 and 1902).

Female Sexual Functions.—There is no evidence that these are injured by smoking. During lactation, insignificant traces of nicotine pass into the milk.

Feeding diets with 0.025 per cent of nicotine to female rats alters the *estrus cycle*, probably as a result of the gastro-intestinal disturbance (R. H. Wilson and DeEds, 1937). Behrendt and Thienes, 1932, obtained no disturbance of the estrus cycle, or of skeletal growth. *Toxic doses* (0.1 mg. per Kg.) administered to rats daily for a month tend to prevent pregnancy, or the young die early. This has been attributed to catarrhal inflammation of the uterus and tubes. The ovaries appear normal (Sodano, 1934). *Injection of subconvulsive doses* into rats, twice daily for six to twelve months, decreases fertility, and the progeny are also less fertile than those from unpoisoned parents (Thienes, Lombard *et al.*, 1946).

Longevity.—R. Pearl, 1938, finds that statistics show a significant deleterious correlation with the amount of smoking: Starting with the age of thirty years, 81 per cent of nonsmokers survive to the age of fifty; 78 per cent of moderate smokers, and 63 per cent of heavy smokers. But those who are reckless with tobacco are likely to be careless of health in other respects.

Treatment of Nicotine Addiction.—The catalogue of injurious actions to be charged against the abuse of this drug is large; but it must be noted that these are absent with moderate use, and can be abolished if the use of the drug is promptly limited on their first appearance. Actual withdrawal is not always necessary. Limitation in quantity, sufficient expectoration and the avoidance of deep inhalation of the smoke may suffice. Quick total withdrawal does not lead to serious abstinence symptoms, as with morphine (except possibly in some neurotic subjects), although it may disturb the function of the bowels for a few days. The principal point in the treatment is to keep the patients' thought off the topic of tobacco, and to supply the accustomed stimulus to the mouth in some other manner, as by chewing ginger or gentian. The use of tobacco should be avoided or restricted in pathologic conditions in which there are special contraindications to it—in heart and vascular disease, dyspepsia, inflammation of the respiratory tract, and so forth.

Other Active Constituents of Tobacco Smoke.—Nicotine alone is responsible for the systemic effects of tobacco smoke; the effects on animals and organs, on the heart, blood pressure, respiration, striped muscle and others agree qualitatively and quantitatively. Other active substances are formed in the combustion, but their quantity is too small to be significant. Nor is there any foundation for the popular notion that commercial cigarettes contain opium or other narcotics (Thurston, 1915).

Other toxic combustion products vary considerably according to conditions. Lee found in the smoke of 100 Gm. of tobacco, besides 1.165 Gm. of nicotine, the following: pyridine bases, 0.146 Gm., chiefly pyridine and collidine; hydrocyanic acid, 0.08 Gm.; ammonia, 0.36 Gm.; CO, 410 cc. *Carbon monoxide* is the most abundant of the toxic constituents of tobacco smoke, aside from nicotine; but Haggard and Greenberg, 1934, state that a person walking on a street with heavy automobile traffic would show a higher percentage of CO hemoglobin than after heavy smoking. Even when many persons smoke in a confined atmosphere, the CO of the air would not rise to more than $\frac{1}{100}$ per cent, and at most 5 per cent of the hemoglobin would be bound to carbon monoxide, according to the U. S. Bureau of Mines. The *hydrocyanic acid* in the smoke of a cigar amounts to only 0.002 to 0.5 mg., and would have no significance (Lehmann and Gundemann, 1912). The quantity of the *pyridine bases* is so small that the amount formed from a dozen cigars would not be materially toxic (Lehmann, Arch. J. Hyg., *68:* 319. The paper describes the separation of nicotine from its decomposition products). The *volatile oils*, which constitute the aroma of the tobacco, are practically inactive. *Menthol cigarettes* are ordinary cigarettes made from tobacco sprayed with a menthol solution. *Arsenic* is sometimes present in harmful quantities when Paris green has been used on the plant as an insecticide. *Free ammonia*, about a third as much as nicotine, is present at the burning end, which is therefore alkaline, but it is bound in passing through the tobacco, and the smoke which reaches the mouth is acid (Bailey and Petre, 1937). Cigarette smoke also contains *aldehyde* and *furfurol*, especially with American tobacco, but the amount is probably not sufficient to be materially irritant, for irritation also occurs when these are low (Bogen).

Acrolein may be formed from the combustion of the glycerol generally added to cigarette tobacco as a hygroscopic agent. Mulinos and Osborne, 1934, reported animal experiments, and F. B. Flinn clinical observations, to show that this is responsible for the acute local irritation, and that the latter was much less for cigarettes moistened with diethylene glycol. With more exact quantitative comparisons, however, H. B. Haag, 1937, and Holck and Carlson, 1937, found that the presence of glycerol in cigarettes did not render their smoke more irritant. *Cigarette paper* does not form toxic combustion products (Wenusch and Schoeller, 1938).

The **nicotine content of tobaccos** ranges between 1 and 8 per cent of the dried leaf. In Havana and Maryland, 1.5 to 3; Virginia and Kentucky, 6 to 8; South American, 2 to 6; German, 1.5 to 3. A number of other alkaloids have been announced to exist in small amount in tobacco (Pictet and Rotschy, 1901), and there is a volatile oil developed in drying and "sweating." The dried leaves were formerly official, but are now obsolete in medicine; if used, an infusion may be made. The dose was given as 0.5 Gm. *Commercial tobaccos packaged for consumption* contain the nicotine median and range shown in the following table (E. M. Bailey, Noland and Mathis, 1928). This also gives the figures for the so-called (and miscalled) "denicotinized" tobaccos:

	Ordinary Brands (Percentage)	*"Denicotinized" Brands (Percentage)*
Pipe tobaccos....	1.95 (1.45–2.84)	0.98 (0.97–2.26)
Cigars..........	1.38 (0.91–1.80)	0.91 (0.67–1.54)
Chewing tobaccos	1.90 (1.06–3.11)	0.95 (0.95–2.10)

Snuff contains 0.29 to 1.17 per cent of nicotine; the daily consumption by confirmed users furnishes 20 to 60 mg. of nicotine (D. Goede, 1944).

The nicotine percentage of American brands of *cigarettes* is given by Bogen, 1929, as

	Percentage
Domestic............................	average 2.5
Blends............................	1.5 –2.5
Oriental............................	1.25–1.5
West Indies	1
"Denicotinized".....................	0.9 –1.4*

* The last figure from C. F. Bailey and Petre, 1937.

Denicotinization.—The methods of removing nicotine from tobaccos spoil its aroma (Storm van Leeuwen, 1918), and the commercial brands do not carry the process far enough to make a significant difference in the effects. Clinically, the stimulation of gastric secretion in hyperchlorhydria is not suppressed (Bernay and Faure, 1937). A small wad of loose cotton in the holder filters out about half of the nicotine, and is quite as efficient as any of the commercial devices, which aim to fix the nicotine by tannic acid or ferric chloride (H. Beer, 1931).

Nicotine Content of Tobacco Smoke.—Not all the nicotine passes into the smoke; a part is burned, depending on the dryness of the tobacco, and another part is condensed in the stub or pipe stem, depending on the length of these. Not all that passes into the smoke is aspirated, a part going into the air between aspirations, depending on the rapidity of smoking; and not all that is inspired is absorbed, a part being expired, depending largely on the depth of the inhalation.

Nicotine exists in tobacco mainly in the form of salts of organic acids (Garner, 1908), especially as acid malate and citrate (Kissling). By the heat of smoking, these are largely dissociated, part of the nicotine being burned and part passing into the smoke as free nicotine (Lehmann, 1909).

Moisture.—The drier the tobacco and the greater the heat, the less nicotine will escape destruction. Moist tobacco, especially cigars, therefore, produce severer effects. This is more important than the nicotine content of the original tobacco (Lee, 1908). The smoke of a moist cigar contains 50 to 75 per cent more nicotine than with the same tobacco in a dry cigar (Heinz), but generally 84 per cent or more of the nicotine of a cigar passes into the smoke. With cigarettes, practically all the nicotine may pass into the smoke, without oxidation or decomposition (Nagy, 1932), presumably because their looser texture facilitates aspiration.

Condensor Effect of the Stub.—As a cigar or cigarette is smoked, the stub becomes much richer in nicotine (three or four times, Lehmann), as well as in tar, for these are condensed there in large degree by the cooling and the filtration of the condensed droplets. The temperature of the smoke falls to that of the room when it has passed through half the length of a cigarette; that of a short stub may rise to 60° C., 140° F. Consequently, the smoke becomes progressively richer in nicotine as the stub shortens. If not more than two-thirds of a cigarette is smoked, about two-thirds of the nicotine and tar is retained by the stub (Malinos and Cockrill, 1938). Winterstein and Aronson found 24.5 mg. of nicotine in the smoke from the first third of a cigar, 29 mg. from the middle third and 46 mg. from the last third. C. O. Jensen and Haley, 1935, recovered 6 per cent of the nicotine of cigarettes from the smoke if four-sevenths of the length was smoked; 11.5 per cent if five-sevenths was smoked, and 17.5 per cent if six-sevenths was smoked.

The *speed of smoking* increases the amount of smoke inhaled, as compared with that which escapes directly in the air from the burning end. For instance, Bogen, 1929, found that when a cigarette was smoked to two-thirds of its length in ten minutes, 0.2 mg. of nicotine was inhaled and 9 mg. escaped; if smoked in five minutes, 2 mg. were inhaled and 4 mg. escaped; if smoked in two minutes, 6.5 mg. were inhaled and 1.5 mg. escaped. *Inhaling smokers* absorb and excrete about ten times as much nicotine as do those who do not inhale (Haag and Larson, 1942).

The preceding data are based on chemical methods which do not actually identify the nicotine. This may be done quantitatively by the blood pressure rise produced by solution of the smoke. By this means, and with intermittent smoking, cigar smoke contains 160 to 425 mg. of nicotine per 100 Gm. of cigar consumed. "Light" and "heavy" cigars do not show constant differences. So-called "nicotine-free" cigars yield as much nicotine in the smoke as ordinary tobacco (Storm van Leeuwen, 1918).

Absorption of Nicotine from Tobacco Smoke.—With ordinary smoking of cigarettes, a fifth to a third of the aspirated nicotine is fanned out with the expired air. The remainder, 60 to 80 per cent, is absorbed chiefly from the dorsum of the tongue. Of the smoke inhaled, the absorption amounts to 93 to 95 per cent (Bodnár *et al.*, 1935; I H. Pierce, 1937).

Under average conditions, the amount of nicotine which enters the mouth in smoking a cigarette (leaving a stub) ranges from 1.8 to 8.5 mg. *The amount absorbed*, with ordinary smoking, ranges from 1.4 to 3.3 mg.; and with inhalation, 1.7 to 8 mg. (Asherton, 1919; Bodnár *et al.*, 1935; I. H. Pierce, 1937). *Deep inhalation* therefore secures stronger nicotine action, and may render cigarettes more harmful than other forms of smoking.

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LOBELIA AND LOBELINE

The herb Lobelia inflata was used by the American Indians as a substitute for tobacco. It was introduced into medicine by Samuel Thompson about the beginning of the nineteenth century as the main basis of his peculiar system of treatment. The chief constituent is the alkaloid *lobeline* with actions closely resembling those of nicotine (Edmunds, 1904). A brand of this alkaloid, "*alpha lobeline*," has been recommended for emergency respiratory stimulation, but safe doses are not reliable and effective doses are not safe. Clinically, the stimulation is transient (at most half an hour), and is often complicated by nausea and vomiting, sometimes with severe collapse and Cheyne-Stokes respiration (Norris and Weiss, 1927; W. R. Marshall, 1928). Large doses are convulsant. There are also two other alkaloids (B base and lobelidine) with apparently identical but somewhat weaker actions.

Oral administration of lobelia has also been employed in respiratory affections, especially in chronic emphysema, spasmodic croup and spasmodic bronchitis. It is a nauseant expectorant, but deranges digestion. As emetic it is effective, but not sufficiently safe.

Respiration and Circulation.—In animals, *intramuscular injection* of lobeline, 0.5 to 5 mg. per Kg., results in marked increase of respiration, slowing of the heart and rise of blood pressure (Van Leeuwen, 1917). These effects are analogous to those of nicotine, and are caused chiefly by reflexes from the carotid body. Large doses involve the centers directly (Heymanns *et al.*, 1932; Comroe, 1938; C. F. Schmidt and Comroe, 1940). Cisternal injection also causes powerful stimulation of the respiration (Janossy, 1925). *Intravenous injection* (clinically, 1.5 to 3 mg.) produces immediate stimulation of the respiration, but also strangulation, coughing and intestinal contraction (Frankati, 1929). Large doses produce convulsions and paralyze the respiratory center and the cardiac muscle (Muto and Iwakawa, 1910).

Efficiency in Respiratory Depression.—In *animals*, large doses of lobeline (2 to 5 mg. per Kg.) overcome the respiratory depression of morphine, though somewhat less effectively that of the aliphatic narcotics (Wieland and Mayer, 1922). The response, however, is not certain (Meissner, 1923). The stimulation passes off within half an hour, and the narcotic depression returns, complicated by the depressant effects of lobeline (R. G. Smith, 1928). *Clinically*, successful results have been reported against depressant poisons (morphine, hypnotics) and in pneumonia, laryngeal stenosis, asphyxia of the newborn, and the like (Eckstein, Rominger and Wieland, 1921, and others). The maximum hypodermic dose of the crystallized ("alpha") lobeline is 10 mg. for adults, 3 mg. for children, which is considerably smaller than the doses found necessary in animals, justifying doubt as to the interpretation. The dangers have been mentioned. Intravenous injection has been used, with one-third of the hypodermic dosage, but Wieland and Mayer warn against this.

The bronchial muscle responds to lobeline with slight initial constriction in living cats (Curtis and Wright, 1926). It has no direct effect on excised bronchi, but prevents contraction by pilocarpine, acetylcholine and arecoline (Björkman, 1926).

Excised Intestines of Rabbits.—Small doses of alpha lobeline produce transitory increase of tonus and amplitude, followed by depression and, with large doses, by paralysis (Antal and Gömöri, 1927).

Lobeline against Tobacco Habit.—J. L. Dorsey, 1936, recommended oral administration of lobeline sulfate (8 mg. in capsule), whenever the desire to smoke is experienced. The intense nausea would generally discourage smoking, but it often proceeds to gastric distress, vomiting and circulatory disturbances, too drastic to render the treatment advisable (I. S. Wright and Littauer, 1937).

Poisoning.—The symptoms are often alarming but rarely dangerous, because emesis nearly always occurs. Many of the specimens of the dried drug are almost inactive. Poisoning is treated by gastric lavage and stimulants.

CONIUM

Conium or "Water-Hemlock," an Umbelliferous herb, contains a number of alkaloids, of which *coniine* is the most important. This is dextro-x-propyl piperidine, and was the first alkaloid synthesized. Children are sometimes poisoned by eating the root. The juice is believed to have been the poison administered to Socrates. It was introduced into medicine by Stoerck, 1770, but is now practically obsolete. It was used as sedative and antispasmodic in chorea, mania, convulsions, whooping cough and asthma; and locally in hemorrhoids and other anal lesions. Its peripheral actions are similar to those of nicotine, but it produces more pronounced paralysis of the central nervous system and of the skeletal muscle nerve endings. Poisoning is treated by tannic acid, evacuation and stimulants. Its actions on the *excised intestines* are also similar to those of nicotine (Ikeda, 1916). It produces initial stimulation and subsequent depression of the *autonomic ganglia*, abolishing the response to cardiac vagus stimulation and the pressor response to nicotine (Linegar *et al.*, 1943). These effects are also produced by piperidine. Dimethyl piperidines depress without stimulation, and do not contract skeletal muscle, as do piperidine and conessine (Koppanyi and Vivino, 1946).

Lupines have some importance as poisons of grazing stock. They contain bitter alkaloids, one of which appears to be related to coniine (C. D. Marsh *et al.*, 1916).

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LATHYRISM

The eating of the peas of Lathyrus produces in man paralysis of the legs which may be permanent if the consumption is continued (Stockman, 1917). Small local outbreaks have occurred frequently in southern Europe (Stockman, 1929), and in east India, where these peas constitute a third to half the diet during two or three months (T. C. M. Young, 1927). The pea contains small quantities of two active alkaloids with identical central effects: motor paralysis, apparently cerebral; increase, then decrease, of spinal reflexes. Both weaken the heart. One also produces a curaroid effect on skeletal muscle endings (Dilling, 1920). Acton and Chopra, 1925, attribute lathyrism to amine bases.

Similar effects are produced by other legume seeds, including lentils and ordinary peas, when they are eaten in large quantities or when purified extracts are injected hypodermically. The poisonous principle is apparently identical, an acid. It produces degeneration of nerve cells and fibers in the brain and spinal cord. Small doses are stimulant; larger, narcotic, similar to opium, coca and tobacco (Stockman, 1931).

Sweet peas (Lath. odoratus) produce lathyrism when liberal quantities are added to the diet of rats. The toxic factor is extractable by boiling water and is not destroyed by prolonged cooking (B. Y. Geiger *et al.*, 1933).

Favism is a clinical syndrome caused by the ingestion of the seeds or "broad bean," *Vicia fava*, occurring chiefly in Sardinia, Sicily and Calabria. It consists in sudden hemolytic attack, the red count falling to 1,000,000 to 2,000,000, with marked leukocytosis, followed by hemoglobinuria and jaundice. The attack lasts two to six days and is rarely fatal, except in children. Autopsies show intense reaction of the reticulo-endothelial system, hyperplasia of the bone marrow and acute swelling of the spleen. The picture resembles that of quinine hemolysis. Passive transfer tests indicate allergy with sensitization by milk (A. A. Luisada, 1941).

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GELSEMIUM

This, the root of Yellow Jasmine, acts similarly to nicotine and coniine. Its central depressant action is more marked (Cushny, 1892). It contains a crystalline alkaloid, *gelsemine*, with weak strychnine action; and several amorphous alkaloids, *gelseminine* and *gelsemoidine* (C. W. Moore, 1910; Sayre, 1910 and 1912; Sayre and Chillingworth, 1914), which are chiefly responsible for the effects of the drug. "Gelseminine" Merck has been shown to consist of gelsemine. Stevenson and Sayre, 1915, describe a further alkaloid, "sempervirine."

The actions of *gelsemine* and *dihydrogelsemine* are quantitatively similar. They relax the rabbit intestine and contract rabbit uterus (F. G. Henderson and Chen, 1943). Gelsemine produces a sharp vasodilator fall of blood pressure on intravenous, but not on intramuscular, injection. It abolishes the response to electric stimulation of the cardiac vagus and the vasodepressive response to acetylcholine. It does not abolish the pressor response to nicotine (Linegar *et al.*, 1943). It produces reversible depression of the excised *heart* of frogs. This is antagonized by barium or epinephrine, not by atropine (Moisset de Espomes, 1938). *Gelseminine* depresses the tonus and contractions of excised intestine (Ikeda, 1916). On intravenous injection of *gelsemicine* there is a latent period of three to thirty-five minutes, followed by depression of the motor neurons of the brain and spinal cord, resulting in respiratory arrest. The vagus is not affected, but sympathetic stimulation is suggested by mydriasis, intestinal relaxation and uterine stimulation (K. K. Chen and Chou, 1939).

Therapeutic Uses.—Gelsemium (1 to 10 drops of the fluidextract) is employed in neuralgic conditions, especially trigeminal neuralgia, nervous headaches, cerebral hyperemia and hysteria. There is no pharmacologic explanation of these uses. Its local application to the eye dilates the pupil, but produces considerable irritation (Putzeys and Romie, 1887). It is no longer used as a mydriatic.

Toxic Effects.—Small doses sometimes cause toxic symptoms, which may be delayed for hours. The warning signs are ptosis, double vision, dilated pupils, weakness and depression. Fatal doses produce slowing and arrest of the respiration. A drachm of the fluidextract is said sometimes to cause death, and 30 minims are dangerous. Poisoning is *treated* by evacuation, atropine and stimulants. The *standardization* is discussed by Pittenger, 1923.

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SPARTEINE

This alkaloid, isolated from Scoparius (Broom top), has been used to slow the pulse in cardiac disturbances, but its effects are uncertain, it weakens the heart, and can not take the place of digitalis.

Sparteine is a pyridine derivative, like nicotine and coniine, and has similar actions (Fick, 1873). Its central effects are slight and its toxicity relatively low (Griffé, 1886, took 0.4 Gm. without bad effects, except slight confusion). It has no direct action on the vasomotor center, but the depression of respiration tends to produce asphyxial stimulation (Pilcher and Sollmann, 1915). Peripherally, it has a fairly strong curare action, arresting respiration by paralyzing the phrenic endings (Cushny and Matthews, 1895). Larger doses also paralyze the respiratory center (Muto and Ishizaka, 1903). Like coniine and piperidine, it depresses autonomic ganglia, abolishing the response to cardiac vagus stimulation and the pressor response to nicotine; it intensifies the pressor response to epinephrine (Linegar *et al.*, 1943). It has a weak local anesthetic effect (Guinard and Geley, 1894). No habituation could be induced in guinea pigs (Dorlencourt, 1913).

Uses.—Sparteine was recommended by Sée, 1885, in cardiac disease, valvular and functional, nervous palpitation, Graves' disease, asthma, and the like. Clarke, 1887, claimed that it produces marked slowing and strengthening of the pulse, the effect appearing in thirty minutes and lasting for five to six hours. Probably most clinicians consider it useless (Leo, 1887). It is devoid of the cardiac tonic action of digitalis, and without this the slowing would be of little value. The influence of drugs on functional cardiac neuroses is difficult to judge.

Circulation.—The experimental data on mammals are variable and confusing. *Small doses* produce peripheral vagus paralysis (Fick and all subsequent workers). This may sometimes result in preliminary quickening of the pulse (Gluzinski, 1889) and removal of vagus arrhythmias (Masius, 1887) and of acetylcholine slowing (Mercier and Hamet, 1931). The vascular effects of acetylcholine are also inverted and potassium actions are reinforced (Hazard, 1939). *Full doses* generally cause slowing and irregularity of the heart. The slowing increases the amplitude of the excursions, but the tendency of the heart is diastolic, in contrast to digitalis (Cushny and Matthews). With intravenous injection, the slowing becomes so extreme that it may be fatal; but this extreme action is of short duration, does not occur on oral administration and is probably due to direct irritation of the endocardium. The *slowing and arrhythmia* with ordinary doses appear to be due to direct depression of the cardiac muscle: They are not prevented by atropine; and electrocardiograms of *excised mammalian hearts* show that sparteine invariably checks the function in all directions (Sakal, 1919). The *frog heart* is stimulated by dilute and depressed by more concentrated solutions, but the effects are slight if the salts of the perfusing solution are properly balanced (Barridge and Seth, 1928).

The *blood pressure* falls progressively, owing to the cardiac depression. The intraventricular pressure is lowered in dogs, and the kidney volume decreases (Duvillier *et al.*, 1922). Perfused ear vessels and coronaries of rabbits are constricted (Romm and Krister, 1931). Cow, 1911, reports that excised arteries are dilated. Rise of blood pressure is sometimes seen (Cerna, 1894), probably due to asphyxia. Sparteine does not antagonize the hypotensive effect of acetycholine (Mercier and Hamet, 1931).

Sensitization to Epinephrine.—Sparteine prolongs the hypertensive effect of epinephrine and tends to restore it when it has been abolished by yohimbine. The mechanism is not clear (R. Hazard, 1932, 1933). Similar "disinversion" is produced by pituitrin (Frohlich and Pick, 1913; Hamet, 1934) and by ephedrine (Hazard and Wurmser, 1935).

Vasoconstrictor Constituent of Scoparius.—Burquet and Vischniac, 1931, reported the production of vasoconstriction of extracts of scoparius, devoid of alkaloids or glucosides.

The **diuretic effect** has been affirmed and denied, clinically and experimentally (MacNider). Its existence is doubtful, but Mercier *et al.*, 1932, reported diuresis and increase of chloride concentration as well as twenty-four-hour output, in dogs. Fronmueller, 1878, contended that the reputed diuretic effect of the parent plant (Scoparius) is due mainly to *scoparine*, a neutral principle.

Respiration.—Moderate doses of sparteine stimulate the respiration and antagonize narcotic depression by a carotid sinus reflex (Zunz and Tremonti, 1931).

Skeletal Muscle.—Small doses of sparteine potentiate the response to indirect stimulation and to acetylcholine. Larger doses have a curarizing action (G. Coppée and Bacq, 1941).

Excised Intestine.—Sparteine depresses the tone and contractions (Ikeda, 1916).

Hemolysis.—Dodel, 1928, reported that sparteine sulfate is a hemolytic agent, and that sodium salicylate protects the corpuscles against this action.

Sparteine Sulfate is hygroscopic and freely sol. in water or alc. Dose, 10 mg., $\frac{1}{6}$ grain, gradually increased to 0.13 Gm., 2 grains, every six to eight hours. Overdoses produce nausea and vomiting.

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GUANIDINE AND METHYLGUANIDINES

Guanidine (imido-urea), $NH:C:(NH_2)_2$, and methyl- and dimethyl-guanidine occur in urine (Kutscher and Lohmann, 1908; Major, 1924). They are closely related to creatine and arginine, and are formed in the putrefaction of proteins. They produce more striking pharmacologic effects than the other nitrogenous metabolites. These effects include fibrillary twitching of striped muscles; with large doses also a curare action; convulsive phenomena and sustained high blood pressure. This suggested that retention of the guanidines might be the cause of clinical tetany (Klinger, 1921), chorea (Fuchs, 1914), eclampsia, and of hypertension (Major and Stephenson, 1925). Since convulsions and high blood pressure can be produced in many other ways, the causative relationship could only be established by the demonstration of effective concentrations of guanidine in the blood. This appears unlikely. The retention of a part of the normal output of guanidine, through impaired kidney function (Major), probably has no greater significance than the similar retention of creatine and uric acid.

Guanidine Derivatives.—A considerable number of these have been studied as to toxicity (Garino, 1916), and especially as to the effect on blood sugar level (Bischoff and Long, 1931). The latter is discussed under *Synthalin.*

Guanidine Substances in Blood and Urine.—These fluids normally contain substances with color reactions strongly suggestive of methyl-guanidine, although their identity has not been definitely established (Andes and Meyers, 1937). In normal males, the daily urinary excretion amounts to 3 to 10 mg. Their concentration in the oxalated blood ranges normally between 0.20 and 0.28 mg. per 100 cc., two-thirds of this being in the cells. It rises to 2.5 mg. per cent in uremia. It is high in *hypertension,* if there is N retention (Andes, Linegar and Myers, 1937). In hypertension produced experimentally in dogs by constriction of the renal arteries, the rise of guanidine bases in the blood parallels the nitrogen retention, without relation to the rise of blood pressure (C. G. Child, 1938). In *normal pregnancy,* it is normal up to and including delivery. It increases to double in three to seven days after parturition and gradually returns to normal by the end of the third week. The postpartum increase is almost wholly in the cells. In severe *pregnancy toxemia,* it may rise (to 0.73 mg. per cent), often accompanied by nitrogen retention (Andes, Linegar and Myers, 1937). Normal values were found in *parathyroid tetany.* Severe damage of the liver by *arsphenamine* did not increase their concentration in the blood, unless there was also severe renal damage (Andes, Hawk and Emerson, 1938).

Fate.—Injected guanidine and methylguanidine are excreted in part unchanged by the urine, but a part disappears. They do not increase the excretion of creatinine, but Wishart, 1920, claims that guanidine injection increases the creatine content of the muscles.

Striped Muscle.—Guanidine greatly increases the sensitiveness of striated muscle to *acetylcholine* (E. Frank *et al.,* 1923). The effects resemble those of nicotine. In excised frog muscle, concentrations above 0.2 per cent produce a *curare-like paralysis;* concentrations between 0.025 and 0.06 per cent cause characteristic *twitchings* (Grant, 1920). These are mainly fascicular; but in frogs, at the height of the poisoning, they are interspersed with contractions of the entire muscles, in regular sequence; and this is the main phenomenon in toads (Frank and Stern, 1921). Gugens and Baumann, 1876, showed that the contractions are peripheral, for they persist after destruction of the central nervous system. Evidence that the action involves the *neuromuscular junction* was furnished by Feng, 1938: A toad sartorius muscle-nerve preparation treated with guanidine responds to a single shock, when applied to the nerve, by a brief tetanus followed by rhythmic twitching; but if the same shock is applied to the muscle, there is but a single twitch. (Guanidine does not produce twitchings if applied directly to a nerve trunk.) The twitchings are abolished by curare and by atropine (Frank and Stern) and do not occur if the nerve endings have been allowed to degenerate (Fuehner, 1920). No twitchings occur if the application is confined to the nerve-free ends of the sartorius muscle, probably because the sarcolemma is less permeable at these regions. The same phenomena are shown by barium and by physostigmine; there is even a potentiated synergism between guanidine and barium (Fuehner, 1920). The guanidine twitchings are suppressed by weakening the muscle (Langley, 1915), and by calcium or magnesium (Fuehner, 1907 and 1911). Local anesthetics (cocaine or procaine) remove the guanidine and nicotine stimulation, but appear ineffective against barium (Frank and Stern, 1921).

Other substances that produce fibrillary twitchings in skeletal muscle comprise: nicotine; parasympathetic stimulants, *i. e.,* physostigmine and acetylcholine; muscular stimulants, *i. e.,* barium, aconitine, veratrine; decalcifying ions, *i. e.,* oxalate, citrate and fluoride; also thiocyanate and some of the metals.

Guanidine, like barium, causes rhythmic contractions of the *melanophores,* synchronous for all these cells in a fish scale, indicating that the action is on a neurofibrillar network, rather than on the end cells, as the latter would not be synchronized by a direct action. This is probably analogous to the muscular twitching (Veil *et al.,* 1932). The *melanophores of frogs* are contracted by methylguanidine, producing pallor of the skin. This is prevented by the previous injection of calcium lactate (Ochoa, 1928).

In **myasthenia gravis,** the administration of guanidine may produce marked and well sustained improvement of muscular function (Dodd, Riven and Minot, 1941), but it fails in many cases. Successful results are attributed to sensitization of the muscle toward acetylcholine. Excessive doses produce nervousness, gastro-intestinal, circulatory and other symptoms, decrease of plasma volume and blood sugar changes. These indicate reduction of dosage, but can be relieved by atropine, and less effectively by calcium (A. S. Minot, 1939), without interfering with the muscular action. A test dose of 10 mg. of guanidine hydrochloride per kilogram of body weight per day should be administered in capsules, and subsequent dosage adjusted to the individual response. It has no effect on other myopathies (A. S. Minot *et al.,* 1939).

Toxic doses fed to animals for several weeks produce changes in muscle metabolism and structure similar to those of muscular dystrophy: loss of creatine and phosphate, severe disturbance of carbohydrate metabolism and electrolytes (R. P. MacFate, 1942).

Guanidine Convulsions.—In mammals, general clonic convulsions are more conspicuous than localized twitchings. With hypodermic injection, there may be a latent interval of an hour; similarly with methyl- and dimethlguanidine.

Cisternal injection in dogs results in marked and prolonged rise of blood pressure and muscular twitchings, greater than with equal doses by vein. They are controlled by cisternal injection of calcium (Resnik and Mason, 1936).

Calcium and Phosphate Equilibrium.—Injection of convulsive doses of guanidine into rabbits greatly increases the phosphate of the serum, and the calcium of the serum is generally somewhat decreased (Watanabe, 1918). The blood calcium is lowered in methylguanidine poisoning, as in parathyroid excision (Bayer, 1922). Repeated injections of sublethal doses of guanidine do not cause calcium deposition in rachitic rats, or decalcification of formed bone (Burns, 1929).

Blood Pressure.—Intravenous injection of guanidine (0.1 to 0.4 Gm. per Kg.) or of methylguanidine produces an immediate large rise of the blood pressure, which is sustained for one-half to four hours (Major and Weber, 1929). In man, 0.05 to 0.08 Gm. per Kg., by vein, raises the systolic pressure by 30 to 50 mm. for about an hour.

The rise is apparently caused by vasoconstriction, through a peripheral action, for it occurs on perfusion (Rothberger, 1902), and the decrease of limb volume is not altered by section of the nerves or of the spinal cord. It is prevented by ergotoxine (H. Goldblatt and Karsner, 1933). The pressure rise occurs before the muscular twitchings. It may be lowered temporarily by nitrites, and more permanently by the injection of calcium and potassium (Major and Stephenson, 1924, 1925). The *heart rate* is slowed during the rise of blood pressure. With intravenous injection of methylguanidine up to 25 mg. per Kg., the inhibitory response to electric *vagus stimulation* is often increased; with 50 to 60 mg., it is temporarily decreased; and with 100 mg., there is generally slowing without vagus block and other cardiac irregularities, and sometimes profound diminution of vagus response (Potter and Stoland, 1932). With *frog heart*, weak concentrations of guanidine and methylguanidine increase the height of the systole; higher concentrations produce diastolic arrest (G. Rosenow, 1921).

Guanidine Shock.—Dogs poisoned with guanidine gradually develop circulatory failure to shock level, with loss of plasma volume. This may be prevented by atropine and less effectively by calcium (A. S. Minot, 1939). The mechanism is not clear.

The **respiration** is greatly slowed, to four or five per minute, and is arrested by larger doses. The animals may be saved by artificial respiration (Klinger, 1921; Major; Major and Stephenson). Guinea pigs are rendered dyspneic by 0.01 Gm. per Kg., and killed by 0.03 Gm. per Kg. The dyspnea gave rise to the theory that methylguanidine was the active agent in *anaphylaxis* (Heyde and Vogt, 1913), but Loewit, 1913, showed the absence of bronchial constriction; indeed, Potter and Stoland, 1932, reported that it produces bronchial dilatation (in dogs); and D. Burns states that guanidine confers *protection* against anaphylaxis if it is injected immediately before or after the provocative dose. Guanidine or methylguanidine, 0.05 per cent, markedly depresses oxygen uptake in various *isolated tissues* (Banu and Gavrilescu, 1934).

The *salivary response to chorda tympani nerve stimulation* is decreased by methylguanidine and completely inhibited by large doses (Potter and Stoland, 1932). *Excised intestines* are stimulated.

Creatinine occurs in urine, but it is controversial whether it exists as such in normal blood, or as a precursor from which it is formed in the kidneys (review, V. C. Myers and Muntwyler, 1940). Creatinine and creatine increase the amplitude of the cardiac contractions in mammals and frog and give some evidence of vasodilatation; but these effects require higher concentrations than exist in life (B. G. Shapiro, 1938).

SYNTHALIN

Guanidine and especially some of its derivatives tend to lower the *blood sugar level;* and this may be pushed to the production of hypoglycemic convulsions, which may be relieved by glucose injection, similar to insulin, although not as effectively (E. Frank, Nothmann and Wagner, 1926). The action has a quite different mechanism, involving damage to the liver function and structure (Boedeker and Junkersdorf, 1931) with exhaustion of the hepatic glycogen (Staub, 1928), which may be preceded by temporary hyperglycemia (Simola, 1927). The nature of the alteration in the carbohydrate metabolism is not understood (Lublin, 1927; Staub, 1928; Kauffmann and Valisco, 1931). Acute nephritis has been observed (Blatherwick *et al.*, 1927; Kawetal, 1929).

One of the more effective derivatives, decamethylene diguanidine, was tried by E. Frank *et al.*, 1926, in diabetes, under the name of "*synthalin*," and most of the clinical and experimental data refer to this product. (In 1928 they introduced the dodecamethylene diguanidine as synthalin B, as being less toxic; but the differences are not essential.) They reported relief of the diabetic symptoms, after oral doses of 50 mg. twice daily for several days, the action being slower but more prolonged than with insulin (as would necessarily follow from the mechanism of its action). It was found unsatisfactory, however (Umber, 1927). The restoration of the blood sugar level is generally imperfect; in dogs, also, it is effective only if the pancreatectomy has been incomplete (Ralli and Tiber, 1929). On the other hand, it causes serious side actions, gastro-intestinal disturbance and nervous depression (in contrast to the relief by insulin), nephritis and hepatitis when continued for a few weeks (Karr, Belk and Petty, 1929). Other guanidine derivatives have been investigated by Bischoff *et al.*, 1929 and 1931, but none is promising, since the liver damage and toxicity closely parallel the hypoglycemic action. Other pharmacologic properties of synthalin were studied by Junkmann, 1927; their toxicity by Simola, 1927. It is a strong protoplasmic poison and antiseptic (Staub, 1928).

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CURARE

This South American arrow poison paralyzes the skeletal muscles through selective depression of their receptive mechanism. It has no effect on sensory nerves and is not an anesthetic. It produces a number of side effects, resembling nicotine in depressing autonomic ganglia (vagus); and strychnine in stimulating the spinal cord. It may produce glycosuria. Intravenously, it causes temporary fall of blood pressure, which returns rapidly to normal with moderate doses. Death occurs by paralysis of the respiratory muscles; animals may be saved by artificial respiration, the drug being rather rapidly excreted by the urine. Curare is mutually antagonistic with physostigmine. It is much less toxic by the stomach, on account of slow absorption and rapid destruction and excretion. It diminishes the response to tonic impulses before it affects brief contractions, as those of voluntary action and of respiration. Carefully graduated doses of standardized preparation are used therapeutically to mitigate the convulsions of the "shock treatment" of mental diseases; to secure muscular relaxation in surgical anesthesia, especially by cyclopropane and pentothal; to relieve proprioceptive spasticity in tetanus, in encephalitis and poliomyelitis;

and as a diagnostic agent in myasthenia gravis, by the exaggerated response. The margin of safety is rather narrow, but standardized preparations appear safe. The erythrina alkaloids and quinine methyl derivatives have a similar or identical action and are perhaps safer.

Origin.—Curare, Woorara or Urari comprise several varieties of extracts, prepared by the Indians of northern and western South America as arrow poisons from several plants. They were brought to Europe from Guiana by Sir W. Raleigh, 1595. They vary greatly in composition (certain varieties were supposed, probably erroneously, to contain snake venom), and they deteriorate on keeping, especially if moist, so that commercial curare is a very unreliable drug. The potent alkaloidal ingredients are derived from several Strychnos species and from several genera of the Menispermaceae (R. C. Gill, 1938). The *varieties* are designated by the kind of containers in which they reach commerce. The source of *tube curare* (in bamboo tubes) is said to be *Chondodendron tomentosum* (Menispermaceae). (Another species, M. Scholtz, 1911, was formerly used under the name of *Pareira Brava* as a bitter tonic.) It contains d-tubo-curarine and curine. A purified and biologically standardized solution marketed as "*Intocostrin*" is at present the most reliable curare preparation for clinical use (A. R. McIntyre and King, 1943). *Calabash (gourd) curare* is obtained principally from *Strychnos* toxifera and contains curarine. *Pot* or *jar (Topf) curare* comes from Strychnos Castelnaei and Cocculus toxiferus, and contains protocurarine and protocurine. Gill, 1946, asserts that the Indians put up all varieties of curare in all kinds of containers, and that these classificiations are wholly misleading. All the varieties consist of brown masses, intensely bitter, not wholly soluble in water, more soluble in dilute acid. The *active constituents* are alkaloids. Curarine and protocurarine have the most typical effects, and the latter is probably stronger. Tubocurarine has a much weaker muscle-nerve action, a stronger strychnine effect and increases the heart rate. Curine is devoid of the muscle-nerve action, but first stimulates and then depresses the heart. It can be converted into curarine (Boehm). *Curarine* is related chemically and in actions to strychnine. Its preparation from calabash curare was described by Boehm, 1887, and by L. Lewin, 1923.

Other Arrow Poisons.—A variety of these are widely used among primitive people. They are often bizarre mixtures, but always with a potent ingredient belonging either to the curare, strychnine or digitalis group (Santesson, 1934). One of the South American arrow poisons, used by Colombian Indians is prepared from the latex of a tree, Ogcodeia, with digitalis actions (Uribe and Mezey, 1946).

Paralysis of "muscle-nerve" endings is ordinarily the only symptom of curare poisoning. When the curare is introduced under the skin, it causes total loss of proprioceptive tonus, then of the voluntary and finally of the respiratory movements. The phenomena appear analogous to myasthenia gravis.

Sequence.—In man, on intravenous injection of the ordinary clinical dose, the effects begin within two minutes, as haziness of vision, followed by ptosis, relaxation of the face muscles, sensation of tightness in the throat, huskiness of voice; then inability to raise the head, next the arm and leg; finally shallowness of respiration. The peak is reached in two and a half or three minutes. The sequence is similar in animals: first the short muscles of the toes, ears and eyes; then the limbs, head and neck; finally the respiratory muscles, first the thoracic, then the diaphragmatic, and lastly the abdominal (Chiò, 1912). The muscles which are least affected by curare are those which contain the largest amount of utilizable oxygen, and survive longest after the death of the animal. This supply of oxygen accounts, perhaps, for the lesser susceptibility to the depressing action of curare. The heart is not affected except with much larger doses.

Development of Paralysis.—The first sign of curare action consists in incapacity for sustained effort on repeated stimulation of the nerve; *i. e.*, whereas a single contraction is normal, fatigue sets in more readily than usual (Boehm, 1894). Then the height of contraction is somewhat lowered. Then the current must be strengthened to obtain any response; and finally even the strongest stimulation of the nerve is ineffectual. However, if the sciatic nerve of a cat is stimulated with a tetanizing current, the muscle does not recover from the curare as rapidly as it would without this stimulation (Luco and Rosenblueth, 1939).

The site of action was investigated by Fontana and established by the work of Cl. Bernard, 1857. It is evident that some structure is paralyzed. The paralysis might have its seat in any part of the central nervous system or it might be peripheral. Stimulation of the sciatic does not produce a contraction if the dose has been sufficient. The point of attack must, therefore, be peripheral to the sciatic nerve. This leaves the nerve trunk itself, the nerve endings and the muscle fibers. Stimulation of the muscle directly is effective, so that it is excluded. To decide between the nerve trunk and nerve endings, Bernard placed a mass ligature around the body of a frog, with the exception of the sciatic nerves, and tightened the ligature so as to exclude the lower extremities from the circulation. He then injected the curare. In this manner the peripheral portions of the sciatic nerves and the endings did not come into contact with the curare, and the nerve trunk alone was exposed to the poison. He found that stimulation of the trunk caused normal contraction, consequently that curare had no action on it, thus leaving only the endings. He also proved the point in a simpler manner by ligating one leg exclusive of the nerve, and by placing the muscle of one and the nerve of another muscle-nerve preparation into the solution. Garten, 1912, has shown by careful methods that even prolonged exposure to strong curare solutions does not affect the nerve trunk. Bernard's experiments show that curare acts on a mechanism between the nerve trunk and the contractile mechanism. This was conceived as the "motor end-plate." Further observations showed that its action is not on the nerve endings that degenerate after section of the nerve, but on the receptive mechanism. This is probably localized mainly at the end plate (Langley). The curare appears to be *fixed at the surface* of the cells, the excess being easily washed out. The fixation is completed within a minute, but the action in excised frog muscle progresses for an hour after the preparation has been removed from the solution (R. Boehm, 1910).

Direct stimulation of the muscle (in cats) requires a somewhat stronger current under curare, but not if the nerve has degenerated. Epinephrine also restores the threshold of muscular stimulation. Fatigue increases the threshold (Gruber, 1914). Henriquez and Lindhard, 1920, reported that the contraction of curarized muscle on direct stimulation does not give rise to an action current. This has been confirmed and denied (H. Schafer, 1936). Its significance is not clear.

Potential of Motor End Plate.—Buchthal and Lindhard, 1935, report that curarization is accompanied by disappearance of the marked potential difference which normally exists (either positive or negative) between the end plate and the muscle fiber.

G. Coppée, 1943, concludes that curarizing agents act chiefly on the motor end plates, depressing their response to nerve impulses (but not the liberation of acetylcholine). He suggests that they unite with a radical of an organic complex so as to release its *potassium*, which lowers the excitability of the end plate.

Invertebrates do not show blockage of nerve-muscle transmission by curare, but a central paralytic action (Piotrowski, 1893; B. Katz, 1936).

Dissociation of Chronaxia.—Lapicque reported that curare (and fatigue) increases the chronaxia of the aneural part of the sartorius muscle (other curarizing agents, such as sparteine, do not), and attributed the curare action to the dissociation of the chronaxia of the muscle and nerve (stated to be normally alike, notwithstanding the difference in their rheobase), this dissociation interfering with the transfer of the excitation from the nerve to the muscle. Rushton, 1933, however, found that curarization can be accomplished without raising the chronaxia of the muscle, if precautions are taken to avoid stimulating the intramuscular nerve. This removes the factual foundation of the Lapicque theory. H. Davis and Forbes, 1936, conclude that while there is usually approximate isochronism in the chronaxia of a muscle and its motor nerve, this does not seem necessary for neuromuscular transmission and that dissociation of chronaxia is not necessary for curarization.

Acetylcholine Antagonism.—Curare and all curarizing substances inhibit the tonus effect of acetylcholine on skeletal muscle; physostigmine and neostigmine antagonize curare. Crude curare preparations inhibit serum *choline esterase* (M.M. Harris and Harris, 1941); pure d-tubo-curarine does not, so that it is not concerned in the curare effect (McIntyre and King, 1943). Intra-arterial injection of d-tubo-curarine into denervated mammalian skeletal muscle may produce strong contraction, similarly to acetylcholine (McIntyre, King and Dunn, 1945).

Removal of curare block may be obtained by washing in physiological solution, or by maintaining the circulation; by summation of stimuli (Bremer); by physostigmine or by veratrine (review, G. Coppée, 1941).

Myasthenia gravis **closely resembles curare poisoning in all respects, and myasthenia patients are up to twenty times more sensitive to curare than are normal individuals.** Intravenous injection of a twentieth of the ordinary dose of standardized curare strikingly increases the myasthenic symptoms, so that it serves as a diagnostic test. The test should be terminated in two or three minutes by intravenous injection of 1.5 mg. of neostigmine methylsulfate and 0.65 mg. of atropine sulfate (A. E. Bennett and Cash, 1943).

Relief of Spastic Contractures by Curare.—Langley, 1905 and 1914, showed that the nicotine tonus of skeletal muscle is relaxed by doses of curare, which do not weaken the response to nerve stimulation. Subparalytic doses are similarly effective against Parkinsonian rigidity, against the persistent contracture of traumatic tetanus and against the stiffness of parathyroid tetany (R. West, 1935; Burman, 1939).

The use of curare against convulsive and spastic conditions has been made feasible by the introduction of standardized extracts. It had previously been suggested especially for strychnine, traumatic tetanus and hydrophobia, but involved too much danger of fatal respiratory paralysis.

Mitigation of Convulsions in "Shock Therapy."—Partial curarization, to generalized flaccid motor paralysis, protects adequately against traumatic complications of metrazol or insulin therapy of mental disorders. With intravenous injection of intocostrin, one-half unit per pound of body weight, the effect occurs immediately, with intramuscular injection in fifteen minutes. More is given if necessary, until the patient is unable to raise the head. The ordinary dose of metrazol may then be injected, producing convulsions of the normal type, but much less powerful. The curare effects slowly recede and disappear in fifteen to twenty minutes. The therapeutic results appear as good as those without curarization. No serious accidents have been reported. Any depression of respiration generally lasts less than five minutes without treatment, but all effects can be removed by intravenous injection of 0.5 mg. of neostigmine (1 cc. of 1:2000). Artificial respiration has not been necessary (A. E. Bennett, 1940). Some cardiac embarrassment is reported in about 10 per cent of patients (G. L. Jones and Pleasants, 1943).

Surgical Operations.—Intocostrin, 70 units intravenously, is used to secure muscular relaxation in cyclopropane and pentothal anesthesia (S. C. Cullen, 1944). H. R. Griffith, 1945, employs 100 units; with this dosage, transitory arrest of respiration occurs in about a tenth of the patients. It is treated by artifical ventilation with oxygen for ten or fifteen minutes. Neostigmine should be available, but was never needed.

Ether somewhat potentiates the intocostrin action (W. Schallek, 1946).

In *spastic states of children*, ½ to 1½ units per pound of body weight are administered intramuscularly at four day intervals.

In *acute poliomyelitis*, curare sometimes gives subjective improvement, but the objective response is not encouraging (M. J. Fox, 1946).

Central Nervous System.—In addition to the peripheral nerve-muscle block, curare has central convulsant effects. These predominate in rats and mice (0.5 to 0.75 units of intocostrin per Kg.), while muscular relaxation prevails in rabbits and cats. The convulsions are of the picrotoxin type, and are antagonized by amytal. They occur also on direct application to the central nervous system (R. E. Cohnberg, 1946; also in dogs, McGuigan, 1916).

Curare and the drugs with curare action suppress the

electrical activity of the frog brain (E. P. Pick, 1945). When curare is applied directly to the spinal cord of frogs, it causes typical *strychnine convulsions*. With ordinary methods of administration these are masked by paralysis of the nerve endings. Certain samples, however, cause strychnine convulsions before the typical curare action appears.

In man, intravenous injection of d-tubo-curarine, with artificial respiration, produces no change of consciousness, sensation, appreciation of pain, electro-encephalogram, or any other manifestation of stimulant, depressant or analgetic action of the higher nervous centers, even with doses more than twice as great as those that cause complete respiratory paralysis (S. M. Smith, Brown *et al.*, 1947).

Paralysis of Respiration as Cause of Death.—In cold-blooded animals in which the respiratory exchange takes place largely through the skin, and respiratory movements are unnecessary, the poison is gradually eliminated if the animal is kept in a moist atmosphere. Complete recovery occurs after eight to ten days, except when the dose is excessive, in which case other factors come into play. Warm-blooded animals die of paralysis of the respiratory muscles. If artificial respiration is kept up and the dose has been only enough to produce paralysis, they may also *recover*. The recovery of the respiratory muscle begins immediately, while the sciatic endings require several hours. The effect of the curare increases progressively with the dose: it is as if an increasing resistance were gradually introduced between the nerve and the muscle. The seat of the *respiratory paralysis* is peripheral, for stimulation of the phrenic nerve does not result in contraction of the diaphragm. The respiratory paralysis, if it is not too profound, is promptly removed by *physostigmine;* stimulation of the sciatic also becomes effective again. *Bronchial muscle* is not affected by curare (Trendelenburg).

Autonomic Ganglia.—The vagus, vasomotor, salivary, pupillary, etc., ganglia are depressed, but usually not as strongly as with nicotine. The antagonism to nicotine stimulation indicates that the paralysis involves the ganglion cells. The order in which the ganglia are affected is also the same as with nicotine (Langley, 1918), and has been discussed in the general section on autonomic poisons.

Effects on the Circulation.—If artificial respiration is maintained, the first effect of curare on the circulation consists in a fall of blood pressure, due to peripheral vasomotor depression. The action is apparently on the ganglion cells (Langley, 1918). This is soon accompanied by quickened heart beat, from depression of the vagus ganglia. The depression does not readily pass into paralysis, so that stimulation of the vagus or sciatic is still effective; indeed, the vasomotor reflexes may be increased, through the central action of the curare. Martin and Stiles, 1914, found that the threshold of the vasomotor center is not raised, even by large doses. The reflex depressor fibers are rendered more sensitive (Langley, 1912), or rather, the depressor response is more nearly proportional to the strength of the stimulus, than in normal animals (Martin and Stiles, 1914). These effects on the circulation pass off within fifteen minutes and the circulation returns to normal, while the muscular paralysis persists. They therefore do not seriously interfere with the employment of the drug. *Perfusion of frog's vessels* shows vasoconstriction, which is not modified by absence of calcium (Pearce, 1913).

Vagus.—The peripheral effects correspond to those of nicotine. Electric stimulation of the vagus does not arrest the heart, but it may be slowed, or beat faster (Dale and Laidlaw, 1911). The *vagus conduction* is slow, in the frog heart, analogous to the skeletal muscles (M. Lapicque and Veil, 1916). Perfusion of the *medulla oblongata*, in the turtle, may stimulate the cardioinhibitory center somewhat, but more commonly tends to diminish the sensitivity of the center to other stimulants (Bush, 1920). The *lymph hearts* of frogs are arrested (Bernard).

Sensory nerves are not affected by curare. The reports of early travelers who describe poisoning by curare arrows mention that sensation is not impaired when motion is impossible.

Peristalsis is often increased, partly by asphyxia, but also with artificial respiration. Bidder, 1865, found no direct effect on intestinal or other smooth muscle, even with the largest doses. Ikeda, 1916, with excised intestine found stimulation of the muscle and slight increase of tone.

Urinary Bladder.—Edmunds and Roth, 1920, found that curare, like atropine, failed to abolish the motor response to parasympathetic and sympathetic stimulation in cats.

Pancreatic Secretion.—Curare, in doses which do not paralyze skeletal muscle, suppresses the secretory response of the pancreas to vagus stimulation, but not to secretin (Gayet and Guillaumic, 1934).

Creatine output, which has been considered as an index of the tonic functions of muscle and is supposed to be controlled by the sympathetic system, is not affected by curare, nor does curare prevent the increase by epinephrine, caffeine, etc. (O. Reisser, 1916).

Glycosuria is a frequent but not constant phenomenon (Morishima, 1899). It is not wholly due to asphyxia, for it can not be completely prevented by artificial respiration (Macleod, 1909). The earlier literature is reviewed by S. Weber, 1904. *Insulin hyperglycemia* antagonizes the toxicity of curare, but not the curare effect of cobra venom (Nechkovitch, 1927).

The **epinephrine output** is markedly depressed by curare in the dosage required to paralyze skeletal muscle (Stewart and Rogoff, 1919).

Inactivity by Gastro-Intestinal Canal.—The effects of curare are usually not obtained on oral administration. Experiments (mainly by Bernard) have shown that: (1) It is not destroyed by the gastric juice, pancreatic juice, or saliva. (2) It passes slowly through the walls of the stomach when the epithelium has been killed, and not at all if the epithelium is still living. (3) It is to some extent fixed or destroyed by the liver, for it is much less active when injected into the portal than into the jugular vein. The discrepancy, however, between the gastric and hypodermic dose persists, even when the liver is largely excluded by Eck's fistula; so that the liver destruction can not be very important in mammals (Polimanti, 1914). It is also destroyed *in vitro* by ox bile and by bacteria. In *frogs* the liver is the main agent in the disintoxication: in normal animals fifty times as much curare is required by mouth as hypodermically; the difference disappears completely if the liver is excised; digestion of curare with liver substance destroys its activity. (4) It is rapidly excreted unchanged in the urine. In *mammals* the inactivity of curare by the mouth is due partly to its destruction by the bile and bacteria, but mainly to the capacity for absorption being less than the capacity for its destruction or excretion. If the renal vessels are tied, poisoning occurs readily even when it is taken by the stomach. If very large doses are taken on an empty stomach, sufficient may be absorbed to cause symptoms.

Intocostrin is a purified extract from Chondrodendron tomentosum (marketed in ampuls of 6 and 10 cc.), standardized on rabbits so that each cubic centimeter corresponds to 20 units of a standard drug. The ordinary intravenous dosage in shock treatment and anesthesia is 0.5 unit per pound of body weight; in myasthenia gravis, 0.1 unit per pound. The anoxic fatal dose for dogs is 0.065 cc. per pound; with artificial respiration it is about twenty times higher, 1.3 cc. per pound. The effect is greater if a sublethal dose is again injected on the succeeding day. Treatment by artificial respiration is more effective than prostigmine (F. Cole, 1946).

Curare-like effects from other drugs are fairly common as side actions, but they are often so overshadowed by other actions that they can be elicited only on excised muscle. The *erythrina alkaloids, quinine methochloride* and ethochloride are suitable, however, for the clinical control of metrazol convulsions.

Over thirty synthetic curare substitutes were studied by H. F. Chase and Lehman, 1942, and Chase, Lehman and Richards, 1944. Quinine ethochloride had the most favorable therapeutic index. A. M. Harvey and Masland, 1941, reporting on the clinical side actions, found that crude curare, beta erythroidine and quinine methochloride all produced moderate fall of blood pressure. The erythroidine and quinine compound occasionally resulted in disorientation and mental confusion. Quinine methochloride sometimes caused severe toxic reactions, with vomiting and abdominal cramps.

Quinine methochloride is effective by oral as well as parenteral administration (A. E. Bennett, 1941). It blocks the transmission of nerve impulses to skeletal muscle, and also the response to acetylcholine (A. M. Harvey, 1940). A. J. Lehman, Chase and Yonkman, 1942, report that *quinine ethochloride* ranks high in absolute toxicity, but has the greatest margin of safety. Its curare action is intense but brief, and therefore easily controlled.

Erythrina Alkaloids.—Several alkaloids, erythroidine, coralloidine, and the like, have been isolated in pure form from various species of Erythrina, "Coral tree," small leguminous trees or shrubs growing in Mexico, Central America, Brazil and tropical Asia. Their curare action was demonstrated by Ramirez and Rivero, 1935 (cited by Santesson, 1938). In frogs, 2 to 10 mg. of the alkaloids per kilogram produce a curare paralysis of short duration, but with larger doses it may last four days. In cats and rabbits the muscles also recover quickly from intravenous injections, unless the dosage is so large as to paralyze the diaphragm; in this event, recovery occurs under artificial respiration in less than an hour. Hypodermic administration is also effective. The alkaloids differ in dose and duration of action. They are not excreted in the urine and appear to be destroyed. The action is antagonized by physostigmine. The erythroidines produce strong parasympathetic stimulation, perhaps analogous to that of nicotine (Lehman and Chase, 1942). The isolation and actions are described by Kunna, Kniazuk and Greslin, 1944. *Erythroidine hydrochloride* is being tried clinically in dystonic and spastic conditions and to mitigate the convulsion treatment of schizophrenia. *Beta erythroidine hydrochloride* is injected intravenously, 100 mg. as 3 per cent solution, every ten seconds until the eyelids droop (generally about 400 mg. in all). This is followed immediately by the metrazol injection. The curare effect reaches its peak in one minute and lasts about fifteen minutes, but there is some variability of response. Excessive respiratory depression may be antagonized with 0.5 mg. of neostigmine (J. M. Williams, 1941). Erythroidine may produce intraventricular heart block, sometimes fatal; Chase and Lehman consider its use too dangerous. Its oral administration is reported to have a hypnotic rather than a curare action (M. S. Burman, 1939, 1940).

Curarizing substances belong chiefly to the following groups: (1) *Alkyl quaternary ammonium derivatives:* methyl and ethyl ammoniums, choline, muscarine, probably curarine. (2) *Pyridine derivatives:* piperidine, nicotine, coniine, arecoline, F 933, sparteine. (3) *Tropine derivatives:* atropine, hyoscyamine, scopolamine, cocaine. (4) Strychnine, methylstrychnine and brucine. (5) Cobra venom. (6) Excess of calcium ions. All desensitize striped muscle to acetylcholine; some diminish the sensitiveness toward potassium; but this is increased by atropine and especially by sparteine (review, G. Coppée, 1941). Pilocarpine curarizes frogs, but not cats (Coppée, 1943). Curarizing effects are also obtainable with guanidine (Brown and Fraser, 1869); delphocurarine, Heyl (Kahn, 1909); quinoline, thalline; morphine and related alkaloids; cocaine; camphor in frogs, but not in warm-blooded animals; certain putrefactive ptomaines; products of muscle metabolism; botulism toxin. S. Fraenkel, 1904, attributes the curare action of the *ammonium bases* and related drugs to the stereochemic orientation of the valences. For excised frog sartorius preparations, *strychnine methyliodide* is a more potent curarizing agent than curarine, but it is less effective *in vivo*, because it is promptly excreted (Cowan and Ing, 1934).

Botulism Toxin.—According to Edmunds and Keiper, 1924, all the phenomena of poisoning by the toxin of the anaerobic bacterium Clostridium botulinum are explained by stimulation, then depression, of the receptive mechanism of the parasympathetic and skeletal muscle. The phenomena set in after a latent period of about twelve hours. In striped muscle, a single stimulus through the nerve produces good contraction, but repeated stimulation leads to rapid exhaustion and paralysis. The response to direct stimulation of the muscle is not altered. Death occurs by asphyxia and may be indefinitely postponed by artificial respiration. The recovery of the muscular excitability, however, is so slow that this treatment is not feasible clinically. Physostigmine fails to counteract the paralysis; but pilocarpine antagonizes the parasympathetic effects on the eye and heart. Congo red injection has been successful in animals, but has not been tested clinically. Its dose would be 10 cc. of 1 per cent solution in 5 per cent dextrose, intravenously. The toxin is destroyed by boiling ten to fifteen minutes so that well boiled food is safe. No outbreak from factory canned foods has been reported since 1925. Man and guinea pigs are highly susceptible, dogs and rabbits are relatively tolerant. The curare action can be produced in frogs if these are warmed.

Botulinus toxin has been isolated as a protein of high molecular weight, crystallizing as needles (C. Lamanna et al., 1946).

EPINEPHRINE

Epinephrine (also called *adrenaline, suprarenine* and numerous similar names) is the active principle of the medulla of the suprarenal gland. It is a relatively simple amine derivative of catechol, and can be prepared synthetically. It behaves as a feeble base and may be classed with the alkaloids. Its solutions are unstable unless a preservative is added. Its typical action consists in a highly specific stimulation of the receptive mechanism of the entire sympathetic system, and the effects upon any given organ—whether augmentory, inhibitory or indifferent—correspond with the effects of stimulation of its sympathetic innervation. They were described in the general section on autonomic drugs. Very dilute concentrations may have opposite effects. Epinephrine, ephedrine and their homologs also inhibit the transmission of nerve impulses in sympathetic ganglia (Marrazzi, 1940). The most important practical manifestation of the sympathetic stimulation consists in a high rise of blood pressure, from peripheral stimulation of the vasoconstrictor mechanism of the systemic vessels, and of the accelerator mechanism of the heart. Epinephrine is used locally for arresting hemorrhage and enhancing the anesthetic effects of cocaine; hypodermically, in bronchial asthma; intravenously, tiding the patient over acute circulatory collapse. Epinephrine leaves the blood stream rapidly and is then destroyed, especially in the liver, so that the effects of intravenous injection are of short duration. It is poorly absorbed from mucous membranes, and its absorption from subcutaneous injections is delayed by its vasoconstrictor effect, so that the response is relatively slight, except as regards especially sensitive conditions, such as asthma, or in hypersensitive individuals. Overdoses, intravenously, kill by acute dilatation of the heart. Other phenyl alkylamines, for instance ephedrine and benzedrine, have similar actions, but differ in important respects.

Influence of Dosage on the General Effects.—The results of increasing intravenous doses may be tabulated (Langley, 1901) as: (*a*) rise of blood pressure; (*b*) inhibition of bladder, mydriasis; (*c*) contraction of uterus, vas deferens and seminal vesicles; salivation and lacrimation; inhibition of stomach and gallbladder; increased bile secretion; inhibition or stimulation of internal anal sphincter; (*d*) contraction of erectores pilorum; (*e*) uncertain effect on tunica dartos and on sweat. *The sensitiveness of different functions to epinephrine* in the normal cat is in the following sequence, in the order of greatest to least: liver, glycemia, blood vessels, denervated heart, nictitating membrane, stomach, iris, pilomotor, salivary (S. Chang, 1937).

The *relative potency of adrenergetic drugs* may be measured by their inhibition of synaptic transmission through sympathetic ganglia. By this criterion epinephrine ranks highest, amphetamine and ephedrine relatively low (A. S. Marrazzi, 1946).

Historical.—Epinephrine is identical with the "*chromaffin substance*" (giving a green color with ferric chloride, and pink with alkalis, iodine or chlorine, and taking up chromium salts; Henle, 1865), which was discovered by Vulpian, 1856, in the medulla of the adrenal bodies, and in association with sympathetic cells elsewhere. The suprarenal medulla is a direct outgrowth of the sympathetic system and consists at first of neuroblasts. The cortex is of mesoblastic origin and does not contain epinephrine, but does contain the cortical hormone, corticosterone and choline (Lohmann, 1907). The pressor action of the medullary substance was discovered by Oliver and Schaefer, 1895, and by Czybulski and Symonovicz, 1895. This was followed by many attempts to separate the active principle. The researches of v. Fuerth, 1898, and particularly those of Abel, paved the way to its isolation in crystalline form, which was first accomplished by Takamine, 1901, Aldrich, 1901, and Abel, 1903. Its structural constitution was determined by Jowett, 1904, and its synthesis accomplished by Stolz, 1904, Dakin, 1905, and Flächer, 1908. Extracts of the *retroperitoneal chromaffin tissue* contain epinephrine or a closely related substance, having the typical action on intestinal and uterine muscle (Fulk and Macleod, 1916). Abel and Macht, 1912, found considerable epinephrine (along with the digitaloid bufagin) in the "parotid glands" of the tropical toad, Bufa agua. It does not occur in the ordinary toad.

Chemical Structure.—Epinephrine is dioxyphenyl (pyrocatechol) ethanol-methyl-amine, $C_6H_3(OH)_2$—CHOH—CH_2—$NHCH_3$. Its structure is related to that of tyrosine, and it may perhaps be derived from this or similar amines in the body.

Action of Isomers.—The natural epinephrine is levorotatory. The synthetic base is racemic. The l-component is identical with the natural base. The dextrorotatory base produces qualitatively the same actions, but has only about a twentieth the potency; the racemic mixture, therefore, has about half the activity of the natural base (Cushny, 1908 and 1909). Froehlich, 1909, claimed that the d-base has a much more persistent action.

Related Sympathetic Substances.—Barger and Dale, 1910, showed that peripheral "sympathomimetic action" is not peculiar to epinephrine, but is shared more or less by a large number of primary and secondary amines, the simplest being the primary fatty amines, such as amylamine. The catechol nucleus is a rather unessential constituent, and the action of catechol itself is not related to that of epinephrine. The intensity and specificity of action increase as the amines approach the composition of epinephrine itself. It is noteworthy that the various sympathetic effects and the augmentory and inhibitory stimulations vary independently in these various amines; nor is there any parallelism between instability and activity. Later work is reported by Raymond-Hamet.

1932, Tiffeneau, 1933, Tainter, 1933, and Hjort, 1934. The latter found only two derivatives truly and consistently sympathomimetic. Changes in the phenolic OH have most marked effects. Ephedrine which lacks these groups is much more stable, acts more directly on smooth muscle and is not sensitized by cocaine. The side chains are relatively unimportant.

Effects on Circulation.—The intravenous injection of epinephrine into a normal animal, with intact vagi, produces striking phenomena due to the interaction of vasoconstriction, vagus stimulation and stimulation of the cardiac accelerator mechanism. The blood pressure rises sharply; as it approaches its maximum, the heart beats are greatly slowed. The sensitiveness of the carotid sinus to blood pressure changes is increased (review, C. W. Darrow, 1943). The pressure is not sustained, but returns quickly to normal. The heart beats also return to their former rate, but more slowly than does the pressure. The blood pressure may rise to a high level, especially if the vagi have been divided or paralyzed. In dogs, it may exceed 300 mm. of mercury. The extent of the rise increases with the dose, but not in simple proportion. The main element in the rise is ordinarily the intense vasoconstriction, for the volume of the organs diminishes as the blood pressure rises. The cardiac stimulation, however, is also an important factor, and sometimes is the more important.

Relation of Dosage to Rise of Blood Pressure.—With intravenous injection in atropinized dogs, this is somewhat as follows (from the data of Hunt, 1901, and others): 0.00008 mg. per kilogram = rise of 5 mm.; 0.00025 = 7 mm.; 0.0005 = 15 mm.; 0.0007 = 20 mm.; 0.0017 = 25 mm.; 0.004 = 45 mm.; 0.006 = 66 mm.; 0.03 = 150 mm. The degree of rise diminishes as the initial blood pressure rises, so that the response obeys the Weber-Fechner law (D. M. Lyon, 1923).

Double Peak of Blood Pressure.—A typical blood pressure curve after large doses of epinephrine (1½ to 1 cc. of 1:10,000, by vein) shows (1) a first rise, due essentially to the peripheral vasoconstriction action; (2) a first fall, interpreted as a beginning relaxation of this peripheral constriction; (3) a slight second rise, attributed to stimulation of the vasomotor center, superimposed on the residual peripheral vasoconstriction, for this peak does not occur after decapitation or high section of the cord (McGuigan and Hyatt, 1918); (4) the final fall, probably due to impurities (Weidlen, 1912), presumably mainly choline (Hunt).

The venous pressure is not altered by small doses; it rises with large doses which embarrass the heart (Capps, 1911 and 1913). The rise is due to back pressure from the arterial constriction and not to the contraction of the veins (Burton-Opitz, 1922); which epinephrine also produces. The rise of vein pressure has also been observed in normal men, after the hypodermic injection of 0.4 to 1 mg. of epinephrine (G. Rosenow, 1920).

Velocity of Blood Flow.—Microscopic observation of the mesenteric vessels in living cats shows this to be increased in the arteries for twenty to thirty minutes after intravenous injection of 0.02 mg. of epinephrine. In the capillaries it was increased for five to seventy-five seconds and then decreased for seventy to 225 seconds (Kisch, 1928). The strong constriction in perfusion experiments slows or arrests the flow.

Cause of the Brief Action of Epinephrine.—When epinephrine is injected intravenously, the effects disappear within a few minutes after the injection ceases. This goes parallel with the disappearance of epinephrine from the blood, and is due to the rapid destruction of the substance. Epinephrine is readily oxidized and thus rendered inactive. The oxidation occurs presumably in many tissues, including the blood, but with different velocity. The blood vessels and especially the liver probably have the largest share. The vessels continue to respond practically uniformly and indefinitely to whatever epinephrine may be present in the blood. Its effects may therefore be repeated by repeating the intravenous injection, and they may be rendered continuous by continuous infusion. A uniform infusion maintains a uniform moderate rise of blood pressure for a considerable time.

Differences According to Methods of Administration.—Epinephrine produces practically no systemic effect when administered by mouth, and is uncertain by rectum (Hoskins, 1921), so that it evidently does not pass readily through the epithelium. It is much less effective by hypodermic or intramuscular injection, or from the serous cavities, than it is by intravenous injection. These differences are due to the rate of absorption, and this in turn to the vasoconstriction. With subcutaneous injection, the vasoconstriction may be so complete that the epinephrine must enter mainly through the lymphatics (D. M. Lyon, 1923). The richness of the local vascular supply is an important factor (Fornet, 1922). The interference is less with intramuscular and peritoneal injections (Lappom, 1915) and with intradural injections (Auer and Meltzer, 1918). Injection under pressure in the nasal submucosa may be almost equivalent to intravenous injection (Pilcher, 1914). The placenta appears to be impermeable to epinephrine injected into the mother (Shimidzu, 1920). The unabsorbed epinephrine at the site of the injection is apparently not destroyed, for the local blanching may persist for one to eight hours (root of rabbit's ear, Meltzer and Auer, 1921; scarified skin, Sollmann and Pilcher, 1917). When this epinephrine becomes gradually absorbed it exerts its systemic actions, and the product of degree times the duration of action is not much less than with intravenous injection (Fornet, 1922; Lyon, 1923). The rate of absorption after hypodermic injection may be increased by *massage* (Luckhardt and Koppanyi, 1926). The absorption is slower if the epinephrine is dissolved in oil. This may be utilized when a prolonged action is desired, as in chronic bronchial asthma (Keeney *et al.*, 1939).

The *blood pressure response in man* is usually practically unchanged on oral administration, but marked reactions may occur (Menninger, 1925). Hypodermically, 0.5 to 1.5 mg. give uncertain results, usually a rise of 10 to 12 mm., rarely higher (to 45 mm.). The same doses intramuscularly give a more constant and higher rise, usually 8 to 25 mm., but sometimes much higher, over 90 mm., so as to produce alarming symptoms (Halsey, 1909). In patients with *arterial hypertension,* 1 mg. hypodermically usually lowers the systolic pressure slightly for half an hour, and the diastolic pressure somewhat longer (A. H. Elliott and Nuzum, 1935). Auer and Gates, 1915, found that *intratracheal injection* of epinephrine produces a prompt rise of blood pressure, presumably by aspiration and absorption from the alveoli. If the vagi have been divided, fatal pulmonary edema often follows. This may be prevented by atropine. S. Weiss and Magasay, 1927, recommended intratracheal administration to relieve asthmatic attacks. Even severe paroxysms can be relieved by carrying epinephrine through the skin by *electrophoresis* (H. A. Abramson, 1939). H. Heller, 1933, reports that *cisternal injection* of epinephrine does not affect the blood pressure. *Lumbar injection* of epinephrine may cause muscular spasm and tremor. Injection under the dura or into the substance of the *cerebrum* produces an apparently natural sleep, lasting two to five hours, with regular respiration and reflexes, and fall of temperature (Bass, 1914). Bass does not believe that these effects can be explained by vasoconstriction. *Oil suspension of epinephrine* on intramuscular injection has about the same toxicity as aqueous solution. The onset of symptoms (blood sugar rise, pupillary dilatation and others) is generally delayed with oil, but the duration is not lengthened (B. K. Richards, 1943).

The disappearance of epinephrine from the blood stream after intravenous injection closely parallels the return of the blood pressure (D. E. Jackson, 1909; Trendelenburg, 1910). About 75 per cent disappears from the blood within fifteen seconds after the injection (Weinstein and Manning, 1937).

Persistence of Action if the Concentration of Epinephrine is Maintained.—In excised kidneys, the perfusion flow may be arrested for a long time, sometimes for hours, by a single injection of epinephrine. The stimulation does not give way to "fatigue" or to depression, no matter how much epinephrine is used. In living animals, *repeated injections* of the same dose, in the same animal, give quantitatively the same pressor effect (Bayac, 1905), for at least twenty successive injections (Kretschmer, 1907). Sufficient time must elapse between injections for the circulation to return to normal; otherwise, there will be superposition. *The uniformity of response is not unlimited:* Froehlich and Pick, 1912, found that if large doses are given in rapid succession, the rise becomes less pronounced and finally disappears, although the blood pressure may remain normal. This is perhaps due to an altered distribution of the blood, for Froehlich, 1910, found that a single dose of d-epinephrine, which has a much more prolonged action, may abolish the response to ordinary l-epinephrine. *Epinephrine is not an antigen:* No antibody is produced, even if the (hypodermic) injections are continued over three months (Elliott and Durham, 1906); nor is there any habituation (Pollak, 1910).

Continuous intravenous injection maintains the pressure rise uniform as long as the rate of injection is uniform (Kretschmer, 1907). The blood pressure level rises as the rate of injection is increased, from the minimal effective dose until a maximum is attained. In rabbits, this occurs when the rate of injection corresponds to about 0.01 mg. per kilogram per minute. Up to this point, the destruction must keep step with the injection, else the rise would be progressive. Further injection produces no further rise, but, when the injection is arrested, the return to normal is inverse to the rate at which the epinephrine has been introduced, since it takes a longer time to destroy the excessive epinephrine. L. R. Dragstedt *et al.*, 1934, continued the injection up to fifteen days in unanesthetized dogs. The blood pressure rise was sustained, but gastrointestinal inhibition developed and proved fatal. Samson, 1932, who had also continued the injection into dogs up to thirteen days, found consistently intracellular fatty changes in the liver and in the Henle loops of the renal tubules and altered staining reactions in the anterior hypophysis and in the adrenal cortex. Continuous injection of excessive doses results in shock (N. E. Freeman *et al.*, 1941).

Response of Blood Pressure and Intestines in Unanesthetized Dogs.—Continuous injection raises the blood pressure with smaller doses than are required to inhibit the intestines (C. A. Dragstedt, 1928), but in unanesthetized dogs the intestines may be more sensitive (Dragstedt and Hoffmann, 1928).

Continuous Injection in Normal Human Subjects.—A. E. Koehler *et al.*, 1937, found that 1:50,000 solution of epinephrine injected intravenously at the rate of 2 mg. per hour maintains a uniform rise of systolic blood pressure averaging 51 mm. Hg. The diastolic pressure usually drops below that of the control period. The oxygen of the venous blood is higher, indicating more rapid blood flow, and the skin temperature rises when the injection has lasted an hour, the basal metabolic rate has risen 29 per cent on the average, the blood sugar 141 mg. per cent, and the blood lactic acid 22.3 mg. per cent. When the injection is stopped, the systolic and diastolic pressure drops in a few minutes below the initial control period, but the skin temperature continues to rise, and also the venous oxygen saturation. *Patients with essential hypertension* reacted similarly to basal metabolic rate and blood sugar, but the blood pressure rise averaged higher, with greater and more lasting drop after stopping the injection. *Continuous intravenous injection of epinephrine* can be maintained for days in patients, injecting 1:750,000 solution of epinephrine in saline, at the rate of 20 to 200 drops per minute (M. Friedemann, 1919).

Fate of Epinephrine.—The brief action of epinephrine with intravenous injection is due primarily to its rapid diffusion out of the blood stream, then to its rather slow oxidation in the tissues generally and to a slight extent in the blood.

Excretion plays an insignificant share, for only traces are found in the urine even after large injections (von Fuerth), and the pressor effects disappear even when access to the excretory organs is prevented by clamping the aorta (Jackson, 1909). After oral administration, if precautions are taken to prevent oxidation in the alimentary tract, up to 70 per cent of the epinephrine is excreted by the urine as conjugated derivatives (D. Richter, 1940).

The *oxidation of epinephrine* presents some confusing phenomena (review, K. H. Beyer, 1946). It occurs readily if the saline solution is exposed to air; but quite slowly in the blood and tissues, where it is protected by ascorbic acid and proteins or amino acids (Bacq, 1937), and perhaps other substances (R. G. Smith, 1937), so that it requires enzymatic activation by either amino-oxidase or phenolase, perhaps after demethylation to nor-adrenaline. Some organs inactivate epinephrine by specific enzymes (Rico and Baptista, 1935).

Oxidation may occur in the ortho OH group; or by forming esters in these groups; or by oxidative de-amination of the side chain. It is not known which predominates.

The *phenolase oxidation* (*in vitro*) results first in the red crystallizable *adrenochrome* (D. E. Green and Richter, 1937). This is inactive pharmacologically. It is fairly unstable and can act as a reversible redox system. Its formation is hastened by cytochrome and somewhat by methemoglobin, but it is doubtful whether epinephrine plays a significant part in cell oxidation under physiological conditions.

Tyrosinase oxidation of adrenochrome produces a colorless substance, *adrenoxine*, known only by its properties. It is highly mydriatic, dilates blood vessels, and inhibits the heart and the intestines. It is not modified by atropine, ergotamine or F 933, but is sensitized by cocaine (Heirman and Goddart, 1939). It is also formed when epinephrine is incubated with smooth muscle (Heirman, 1938). Further oxidation *in vitro* results in active *melanins*. These products are also formed when watery or saline solutions of epinephrine undergo spontaneous oxidation (review, Jeanne Lévy, 1939). The oxidation of epinephrine by epinephrine oxidase takes an entirely different course which does not produce adrenachrome and adrenoxine. *Spontaneous oxidation of epinephrine* is especially prompt in dilute and alkaline watery and saline solutions (B. Moore, 1895) with the succession of changes in color and actions that was described for the phenolase oxidation.

Destruction of epinephrine in living tissues proceeds slowly, for instance with subcutaneous injection, or when it is perfused through rabbit's *ear* (A. D. Steinberg, 1935), or through the liver or other abdominal viscera. Gioffredi, 1907, reported the rate of epinephrine destruction especially high in perfused liver. Later investigators, however, found a practically normal rate of pressure fall in animals in which the liver, kidneys, spleen and all the abdominal organs had been removed (Markowitz and Mann, 1929; Weinstein and Manning, 1937). Kretschmer, 1907, found that the destruction *in vivo* is hastened (*i. e.*, the action is shortened) by lessening the alkalinity of the blood by the injection of acids; and *vice versa.*

Blood in vitro has a curiously slow destructive effect, so that the activity is preserved for many hours (Oliver and Schaefer, 1895); indeed, small quantities of serum retard the destruction materially (Schwerschnikoff, 1913), probably by the reducing action of amino acids, glutathione and ascorbic acid (A. D. Welch, 1934). The inactivation in blood or serum is never complete, but proceeds to an equilibrium. It may be completed by adding liver or other tissues (W. A. Bain *et al.*, 1937). Cerebrospinal fluid destroys epinephrine much more rapidly than does serum (Meltzer, 1911).

The *accelerating effect of tissues* is due to phenolase (Blaschko *et al.*, 1937; D. Richter, 1937), and goes through the stages and actions sketched above, which occur also in the spontaneous oxidation of epinephrine solutions. *Sympatholytic drugs* are supposed to accelerate the oxidation (Heirman, 1938; Bacq, 1938; Lissak, 1938; Goffart, 1939).

Formaldehyde and acetaldehyde (not glyceric aldehyde or methyl glyoxal) promptly inactivate epinephrine through its amido group. This action is catalytic and requires the presence of oxygen; it is not prevented by ascorbic acid (J. Cramer, 1911; G. Bayer and Wense, 1938; Malafaya-Baptista and Toscano-Rico, 1935).

Action on Blood Vessels.—The powerful vasoconstriction is the main factor in the rise of blood pressure, for the organ volume and the outflow of blood from veins are diminished. The site of action is almost entirely peripheral, for the rise occurs if the central nervous system has been destroyed; the perfusion flow through excised organs is slowed or arrested (Bier, 1897); and rings of excised artery contract if placed in epinephrine solutions (A. B. Meyer, 1907). The vasomotor center is not usually affected directly; it may respond indirectly, generally by constriction, to the increased pressure; occasionally by dilatation, when the increased blood supply relieves a preexisting asphyxial stimulation (Pilcher and Sollmann, 1915). The sympathetic constriction involves the smooth muscle in arteries, veins and capillaries. Its intensity varies with the relative abundance of the muscular tissue; it is therefore more intense in the arterioles. Important differences exist also in the susceptibility of the vascular area, presumably according to the development of their sympathetic receptive mechanism. The maximum constriction occurs in the splanchnic vessels, especially the kidneys, and in the vessels supplying voluntary muscles and mucous membranes. The constrictor action is weak in the coronary, cerebral and pulmonary vessels; and in the intact animal these vessels are passively dilated by the displacement of blood from the more powerfully constricted areas. Certain vessels are *dilated directly* (Cow), for instance the coronary in man. In others, dilatation occurs only with very dilute solutions, or under special conditions, late in the course of prolonged perfusions, or when the vascular tone is already high. The reactions are also influenced by the presence of other vasomotor drugs. The constriction of susceptible vessels persists as long as effective concentrations of epinephrine are present. Even *very large doses* of epinephrine (7000 times the effective quantity) do not paralyze the vasomotor mechanism. As to *other aromatic amines*, the pressor action in decerebrated animals is greatest with catechol compounds, less with phenol compounds, and least with phenyl compounds (Crismon and Tainter, 1939).

Comparison of Epinephrine Derivatives.—M. L. Tainter (review, 1941) grades these as follows, in descending order of efficiency: *Cardiovascular action on intravenous injection:* Epinephrine > cobefrine > neosynephrine > ephedrine > propadrine. *Adjuvant to local anesthesia:* Epinephrine, 1:50,000, equals cobefrine, 1:10,000, or neosynephrine, 1:2,500. *Decongestion of mucosae:* Prefers ephedrine, 1 to 3 per cent, or neosynephrine, $\frac{1}{4}$ per cent.

Arterial rings are suspended in oxygenated Ringer's solution (A. B. Meyer); better results are obtained if a careful technic is followed (Rothlin, 1921). Epinephrine constricts most arteries, but relaxes some, for instance the pulmonary vessels (Rothlin). The response is usually much greater with a second exposure of the washed artery. This holds true also for other vascular drugs (Rothlin). Epinephrine favors the occurrence of *rhythmic contractions* in the arterial rings. These may also be evoked by other conditions that raise the tone of the arterial muscle, by muscular stimulants (Wachholder, 1921); by oxygen (Helene Friedmann, 1920); and by distention (Bayliss). They are abolished by muscular depressants and by carbon dioxide.

Direct Effect on Veins.—Gunn and Chavasse, 1913, showed that excised veins also react by constriction, although this does not apply to all veins (Crawford and Twombly, 1913). Segments of the superior vena cava, near the heart, enter into rhythmic pulsations. Domenjoz and Fleisch, 1939, studied the responses of perfused veins to drugs with reference to the relation of action to chemical structure. (Active contraction of the veins has also been demonstrated *in situ* by stimulation of the efferent nerves; by reflexes and by asphyxia; Hooker, 1918.)

Perfusion of organs is usually demonstrated on the hind legs of the frog (Laewen-Trendelenburg), but the ear of the rabbit or any mammalian organ may be used to illustrate differences in the reactions of various areas. Morton and Tainter, 1940, compared a series of sympathomimetic amines on perfused cat leg. Epinephrine and other constricting drugs slow or arrest the outflow; nitrites and other dilating drugs quicken the flow. The method is delicate, but is somewhat complicated by the formation of edema. Continued perfusion with Ringer's solution increases the sensitiveness, perhaps by washing out excess acid from the muscles (Alday-Redomet, 1920). Frog legs three days old and distinctly putrid continued to respond to epinephrine. *Prolonged perfusion with epinephrine* may alter the response of the frog legs so that they tend to react by dilatation to increased concentration of epinephrine, and to histamine and pituitary; but preserve their constrictor response to barium, strophanthin and nicotine. Epinephrine thus becomes antagonistic to barium (Bauer and Froehlich, 1918).

Microscopic Examination.—In the frog's foot, epinephrine may be seen to constrict especially the arterioles, and to antagonize local vasodilators, such as sodium barbital (W. Jacobi, 1920). Krogh, 1919, and his pupils and others (Carrier, 1922, and so on) have shown that the capillaries are also involved, and Krogh observed that the action is on the smooth muscle fibers that are sparsely scattered over the capillaries and serve as sluices. They are generally constricted, but may be unaffected or dilated according to the organ and species.

Dilator Action of Epinephrine.—This is the predominant response of certain mammalian vessels (D. Cow, 1911), but may occur in others under special conditions, especially with very dilute concentrations; late in the course of perfusions; and particularly when the vascular tone is already high (Brodie and Dixon, 1904; Ogawa, 1912). In unanesthetized animals, the injection of epinephrine at the estimated rate of normal secretion tends to *raise* the blood pressure (C. A. Dragstedt, 1928). Increase of temperature diminished the contractor response, and at 41° to 45° C. reversed into dilatation. *Frog's vessels* do not show dilatation with dilute solutions, or with increase of temperature, but only in the absence of calcium or after *degeneration of the nerves* (Pearce, 1913). In the *ear of the living rabbit*, the constriction is followed by dilatation, especially on the succeeding day (Meltzer and Auer, 1921). The vessels of the *denervated ear* were said to dilate with doses that are constrictor for the normal ear (Engeloch, 1915), but Meltzer and Auer, 1921, could not distinguish any special difference after denervation.

Cannon and Lyman, 1913, reported that small doses either raise or lower the blood pressure, according to its previous level, and adduce evidence that the lowering is due to a direct dilator action on constricted arterial muscle. The fall occurs after ergotoxine. The dilator reaction is confined mainly to the vessels of the legs, for the fall of pressure which occurs with normal cats (0.002 mg.) occurs also if the splanchnic vessels are ligated, but is replaced by a rise if the splanchnic vessels are intact and the important peripheral trunks ligated (Hartmann, 1915). The dilator reaction fails if the vessels are already relaxed, as by hemorrhage or depressor stimulation. However, Swetschnikoff, 1914, on isolated rabbit's ear, observed the same constriction, whether the pressure was high or low. The vasodilator effects observed in living animals are due partly if not solely to *direct action* on the vascular muscles, for they may occur after complete degeneration of their nerves (Dale and Richards, 1918). In cats the dilator reaction is developed to the full degree only eleven weeks after birth (Hartmann and Kilborn, 1918).

Therapeutic application of the local vasoconstriction is made for the control of capillary hemorrhage, for the relief of congested mucous membranes and to diminish the absorption of local anesthetics.

Epinephrine as a Local Hemostatic.—Solutions of 1:50,000 to 1:1000 arrest capillary hemorrhage in any situation to which they can be applied locally, especially in nasal and laryngeal operations. The dilutions must be freshly prepared, since they lose their activity in a few hours. The action persists as long as the epinephrine is present; but when this has disappeared there is often secondary hemorrhage, if the clot fails to adhere to the dilating vessel. Ephedrine is less liable to such accidents, since its constriction passes off much more slowly. Epinephrine is of little use against venous, and still less against arterial, hemorrhage (Hanzlik, 1918). With high concentrations, the intense and persistent ischemia may cause tissue injury, with delayed healing and even necrosis (Hrubetz, 1933).

On inflamed mucous membranes, epinephrine gives relief by contracting the dilated vessels. It is used in catarrhal conditions, *e. g.*, in *conjunctivitis* and especially in *hay fever*, and to widen the nasal air channel and the entrance of the *sinuses*.

Oily solutions or ointments, containing $\frac{1}{10}$ per cent of the free alkaloid, prolong the action. Epinephrine is nonirritant, but its action is brief, and it is claimed that its continued use has caused chronic turgescence of the mucous membrane (J. N. Hall, 1910). Vasoconstrictors are useful in surgical procedures and in acute sinusitis, but they are reported to lengthen the course of acute rhinitis and to increase the incidence of sinus and ear complications. Allergic vasomotor rhinitis is said to be made more severe by them (B. M. Kully, 1945). Concentrations stronger than 1:4000 should not be used on the conjunctiva, as 1:1000 causes an unpleasant sensation of muscular spasm (Fantus). Against *hemorrhoids* it may be used in suppositories: 1 mg. ($\frac{1}{16}$ grain) of the alkaloid in 1 Gm. of Theobroma oil.

Skin Reaction to Epinephrine.—The intracutaneous injection of epinephrine (a drop of 1:100,000) produces intense blanching and "gooseflesh," persisting for several hours (Sollmann and Pilcher, 1916). The blanching occurs though the circulation of the skin has been obstructed, so that the action must involve the capillaries (Cotton *et al.*, 1916). It was claimed that modifications of this reaction occur in "hyperthyroidism" (Goetsch), but they are not characteristic and are seen in 20 per cent of normal individuals (van Wagenen, 1922).

Differences in the Response of Vascular Areas.—The reaction of different vessels to epinephrine varies quantitatively and somewhat qualitatively, depending on the sympathetic susceptibility. In cats and rabbits, doses large enough to raise the blood pressure cause constriction of the skin vessels and dilatation, chiefly passive, of the arterioles, of the muscles and intestines.

Direct dilatation is revealed by perfusion of excised arteries. The arterioles of the skeletal muscles are dilated by small and constricted by large doses. Those of the skin, bone and spleen are not dilated by any dose. The reactions of other important areas are complex (Rothlin, 1921). When injected directly into the human *brachial artery*, 0.0001 to 0.3 mg. of epinephrine produces constriction of the vessels of the hand and arm with pallor and coldness, similar to Raynaud's disease. It is not effectively antagonized by mecholyl. Amphetamine produces systemic but no local effects (Myerson *et al.*, 1938).

The effects on coronary circulation have been studied extensively. The results appear confusing, partly because the direct action varies in different animals; partly because it is not very strong, and is therefore easily complicated by indirect effects and by differences in experimental methods. Clinically, it probably causes coronary constriction in most cases, and reduces the flow.

Excised coronary arteries respond to dilatation in most mammals, but by constriction in man and monkeys (Barbour, 1912; Barbour and Prince, 1915; Park and Janeway, 1912; and others). *Perfusion of the arrested heart* may cause either dilatation (Elliott, 1905) or weak constriction (Wiggers, 1909). Katz and Lindner, 1939, report dilatation in arrested dog heart, sometimes preceded by slight constriction.

In the beating heart, the coronary flow is increased in most species of animals (excised hearts, Wiggers; Markwalder and Starling, 1913; not in monkeys, Barbour and Prince, 1915) because of the pumping action of the contracting cardiac muscle. In the intact animal, this occurs even if the blood pressure is kept level by hemorrhage (F. Meyer, 1913); and the increase would be still greater if the blood pressure, and therefore the coronary pressure, were allowed to rise (Bond, 1911). In *anesthetized dogs*, epinephrine injection increases the coronary flow, much more than would correspond to the rise of aortic pressure, indicating a weak dilator action on the coronary arteries. This tends to supply the increased metabolic requirements of the augmented heart action; but may not always be adequate to prevent angina (H. D. Green, Wégria and Boyer, 1942). A vasoconstrictor effect on the coronary vessels can be discerned in the excised heart only with doses which are too small to affect the cardiac muscle (Brodie and Cullis, 1911). In the *monkey*, however, and therefore presumably in man, the conditions are different. All doses slow the coronary flow of the excised monkey heart, whether this is beating or resting (Barbour and Prince, 1915). The coronary effects of epinephrine were also studied by Anrep and Stacey, 1927; Ducret, 1930; F. M. Smith *et al.*, 1926.

After experimental occlusion of a coronary branch in dogs, epinephrine and synephrine do not effectively increase the *collateral circulation* (Wiggers and Green, 1936).

The pulmonary vessels show weak vasoconstriction (A. S. Dale and Narayana, 1935). Tribe, 1912, attributed the negative results reported by some investigators to the dilator effect of the chloretone in certain commercial solutions. Barbour, 1912, found that the reaction of arterial rings varied according to their situation; the intravisceral portion of the artery did not react; the extravisceral portion was constricted.

Pulmonary Circulation in Living Animals.—Epinephrine generally causes a large rise of pressure in the pulmonary artery (Wood, Jr., 1911). The response is complex, depending on the species, as well as on dosage and other conditions. With *dogs* and *cats* the cardiac stimulation tends to predominate, so that the pressure rises in both the pulmonary and systemic vessels (Schaefer and Lim, 1919). The volume of the blood in the lungs increases (Anderes, 1915) and the pulmonary circulation is quickened, with moderate doses. Large doses delay the circulation time (Langlois and Desbouis, 1912), either by injury of the heart or by constriction of the pulmonary vessels. When *cardiac dilatation* occurs, the diminished efficiency of the heart causes a further rise of the pulmonary pressure with falling arterial pressure (Hallion and Nepper, 1911). This favors the production of *pulmonary edema.*

Portal vessels are markedly constricted on perfusion, in mammals and frogs (Berezin, 1914), as also in intact animals (Burton-Opitz, 1913). The response is much greater than that to electric stimulation of the nerves (Macleod and Pearce, 1914). Edmunds, 1915, confirmed the constrictor effect on excised portal vein.

Cerebral Vessels.—In *man*, small doses of epinephrine first diminish and then increase the brain volume (Raphael and Stanton, 1919). The dilatation is probably passive. In *animals*, Wiggers, 1914, found constriction; Berezin, 1916, observed constriction, but requiring higher concentration than for peripheral vessels; Dixon and Halliburton claim dilatation. Cow observed slight relaxation of arterial rings. There is undoubtedly passive dilatation in the intact animal (Biedl and Reiner, 1905). The vessels of the pia and retina are constricted (Hirschfelder, 1915). By direct microscopic examination in unanesthetized living animals, Cachera and Fauvert, 1936, observed dilatation of the arterioles by 10 to 45 per cent, and of the veins by 15 to 20 per cent, on intravenous injection of epinephrine. The brain volume increased.

The **renal vessels** appear to be highly sensitive to epinephrine, so that doses too small to affect the general blood pressure diminish the volume of the kidneys and slow their vein flow (Hoskins and Gunning, 1917). Somewhat larger doses may cause dilatation (Ogawa, 1912), which is passive, for if the blood pressure is kept level all concentrations produce constriction (Ozaki, 1927). Ordinary doses diminish the kidney volume. Perfused kidneys are constricted; but if the sensitiveness of the vessels has been dulled by prolonged exposure, they may respond with dilatation (Sollmann, 1905). Direct microscopic inspection of the frog kidney shows swelling of the glomerular vessels when small doses are injected; and shrinkage with larger doses (Richards and Schmidt, 1924). The swelling of the glomerular tufts occurs also if the blood flow is kept constant (A. N. Richards, Barnwell and Bradley, 1927), indicating constriction of the efferent vessels, and thus increased filtration pressure. It has been contended that glomerular filtration in various conditions is regulated almost entirely by the efferent arteries, but the evidence is not clear, and it appears more probable that the afferent arteries may also play a part (H. Lamport, 1941)

Urine Flow.—Small doses of epinephrine, which increase the kidney volume, increase the urine flow (Bardier and Frenkel, 1899; Ogawa, 1912). The diuresis is aided by hyperglycemia (Biberfeld, 1897). The intravenous injection of ordinary doses ($\frac{1}{20}$ mg. per rabbit) diminishes the urine flow and the renal vein flow in direct proportion to the rise of blood pressure (Cushny and Lambic, 1921). Hypodermic injection of large doses (2 mg. per rabbit) produces a strong diuresis that lasts for several hours (Biberfeld, 1907). It is independent of the glycosuria (Konschegg, 1912). In *anesthetized dogs*, intramuscular and slow intravenous injection result in polyuria; rapid intravenous injection causes oliguria with protein in the urine (Toth, 1937).

Cerebrospinal Fluid.—The secretion is not affected, the pressure varying merely with the blood pressure changes (Dixon and Halliburton, 1916; Weinberg, 1933).

Lymph Secretion.—The thoracic lymph flow increases parallel to the rise of arterial pressure; the effect, therefore, is apparently circulatory (Yanagawa, 1916).

Synergisms and Antagonisms.—The actions of epinephrine and the related bases, ephedrine, tyramine, and the like, are altered by conditions, including other drugs, and often show potentiated synergism and antagonism, sensitization and desensitization, and reversal of the normal responses. The modification of the blood pressure reactions is especially characteristic: Previous injection of ergotamine or ergotoxine and of certain dioxane derivatives prevents the response to epinephrine, so that this causes a fall, while cocaine sensitizes to the pressor action. With ephedrine, the corresponding dosage of ergotamine has little effect, and cocaine diminishes and may even reverse the pressor response of ephedrine and tyramine (Tainter, 1929).

Other sympathomimetic amines exhibit various modifications of these synergisms and antagonisms (Raymond-Hamet, 1930, 1931; Schaumann, 1930).

Epinephrine and ephedrine show considerable potentiation on mammalian blood pressure, frog vessel perfusion, and on the uterus. On the other hand, ephedrine may contract a uterus which has been inhibited by epinephrine (O. Schaumann, 1928).

Ergotamine or Ergotoxine Antagonism.—The cause of the actual lowering of blood pressure by epinephrine, after the injection of ergot, the "vasomotor reversal" (Dale, 1905; Sollmann and Brown, 1905), has not been established. It lasts only for a few minutes (E. Polak, 1926). Ergotamine is relatively ineffective against the *ephedrine* rise, and does not cause reversal (De Eds and Butt, 1927), unless the dose of ephedrine is small (Curtis, 1928). The antagonism to epinephrine is also less marked in the *other organs;* for instance, as regards bronchial dilatation (Swanson, 1929). *Anesthetics* markedly influence the vasomotor reversal by ergotamine: This occurs under ether or urethane anesthesia; but in barbiturate anesthesia, ergotamine reinforces the epinephrine rise, in cats and dogs (Herwick *et al.*, 1938). *Quinine and quinidine*

(3 mg. per Kg.) produce vasomotor reversal to epinephrine and to splanchnic stimulation, in dogs and cats; and reversal of the epinephrine stimulation in rabbits' uterus, but they are additive to the relaxing effects of the epinephrine on virgin cat uterus. Most of the other actions of epinephrine are not affected by quinine or quinidine (E. E. Nelson, 1928). *Yohimbine* acts somewhat like ergotoxine, producing blood pressure reversal in dogs toward epinephrine, but only weakening the pressor response to ephedrine (Raymond-Hamet, 1927, 1931). *Corynanthine*, an isomer of yohimbine, occurring in Pseudocinchona africana, has double the sympatheticolytic potency of yohimbine. As local anesthetic it is but an eighth as potent. It is also antipyretic (C. C. Scholz, 1935). *Gambirine* occurring in a Rubiaceous plant is likewise sympatheticolytic (Rothlin and Hamet, 1935).

Cocaine Sensitization and Desensitization.—Cocaine, in doses which have no effect by themselves, greatly increases the response to some of the augmentory reactions of epinephrine, and inhibits others (Froehlich and Loewi, 1910; von Fischel, 1915). The modifications for ephedrine and tyramine are quite different (De Eds, 1927).

The cocaine synergism is probably explained by inhibition of epinephrine oxidation. Cocaine, procaine, stovaine, butyn and percaine all potentiate epinephrine, and all inhibit amine oxidase of rat and guinea pig liver, cytochrome oxidase and catechol oxidase (Philpot, 1940) and phenol sulfur esterase (C. Torda, 1943). The influence of cocaine on some of the principal organs is as follows: *Heart and blood-vessels:* increase of the augmentory response to epinephrine, decrease to tyramine and ephedrine; *uterus* of nonpregnant cat: diminished inhibition by epinephrine and tyramine; *intestines:* diminished inhibition by tyramine, varying effects on epinephrine; *denervated iris:* increased dilator response to epinephrine, not to tyramine or ephedrine; *bronchial dilatation:* increased for epinephrine, decreased for ephedrine and especially for pseudo-ephedrine. *Cocaine alone* dilates the blood vessels of perfused limbs; stimulates the virgin cat uterus and cat intestine; and has no effect on isolated auricle (Burn and Tainter, 1931). *Strychnine* is reported to sensitize to epinephrine similarly to cocaine (Martinetti and Marri, 1939).

The dye *thionin* has no effect on the blood pressure of normal animals, but causes a rise if the animal has had epinephrine within twenty-four hours previously (Gautrelet, 1921).

Parasympathetic drugs generally give simple algebraic summation with epinephrine. *Atropine* antagonizes the epinephrine constriction in frogs, although it has no direct effect alone, nor does it antagonize barium (Hildebrandt, 1920). *Acetylcholine*, like epinephrine, constricts the frog vessels when perfused alone; but the two together produce dilatation (Kolm and Pick, 1920).

Nonspecific Drugs.—Nitrites, caffeine, histamine and sometimes pituitary, antagonize the epinephrine rise. The effect of *nitrite* is almost quantitatively additive. In perfused frog vessels, epinephrine is balanced by one hundred to two hundred times its weight of nitroglycerin (Gramenitzki, 1930). *Caffeine* antagonizes epinephrine in doses which are ineffective on the normal vessels (Sollmann and Pilcher, 1911). Mutual antagonism with *histamine* and *pituitary* was described by Lhosia, 1920. Others found simple summation of the pressor effects with pituitary (Hoskins, 1915). Pituitary injection does not increase, but rather diminishes, the epinephrine hyperglycemia (Stenstroem, 1914). *Sodium bisulfite*, 0.1 to 0.2 per cent, materially increases the toxicity of intramuscular injections of epinephrine, neosynephrine and procaine, presumably by checking their detoxication. It has no effect on ephedrine (R. K. Richards, 1943). *Barbiturates* are reported to augment the vasoconstriction (Busquet and Vischniac, 1938). *Apocodeine* antagonizes the epinpehrine constriction (Brodie and Dixon, 1904). *Spleen extract*, intravenously, increases the pressor response to epinephrine (Collip, 1920). Lendle and Pühlmann, 1939, studied the effect of the *concentration* of various substances on the epinephrine-sensitivity of perfused rabbit ear. They found the response reduced by vasodilating concentrations of narcotics, antipyrine, quinine and caffeine, while capillary poisons, arsenic and borates, reduced the epinephrine response in concentrations which do not cause much change when used alone; adenyl, nitrites and possibly barbiturates required more than dilating concentrations to decrease epinephrine response.

Ion-Ratio.—The constrictor response of the perfused ear of rabbits to epinephrine is increased by reduction of the *calcium* concentration and decreased by either excess or absence of calcium. Changes in *potassium* concentration have little effect (Masago, 1928).

Synergism with Thyroid.—Thyroxin, which by itself evokes no reaction of the blood vessels, sensitizes them to the constrictor action of epinpehrine and to the dilator response of stimulation of the depressor nerve. The epinephrine synergism may also be produced by stimulating the thyroid secretion through the superior laryngeal nerve, or through the cervical sympathetic; but it is local, for it occurs in perfused organs. The pupillodilator reaction is not sensitized (Asher and Flack, 1911; Santesson, 1918). The quantitative reactions of the skin, of metabolism, and the like, to epinephrine have been proposed as tests of "hyperthyroidism," but no constant relations have been established.

Central vasomotor stimulation, pressor or depressor, electric or by nicotine, is diminished or abolished by epinephrine (Oliver and Schaefer), independently of the level of blood pressure (Hoskins, 1915). *Decrease of blood volume* by *hemorrhage, shock or deep ether anesthesia* diminishes the response to epinephrine, and this may be restored by transfusion (Rous and Wilson, 1919).

Cardiac Effects.—In intact animals these are complicated by the vasomotor phenomena. The pulse rate is sometimes slowed, in response to the rise of blood pressure; but the heart tends to escape from the inhibition and to be greatly quickened by direct stimulation of the accelerator receptive mechanism. If the vagi have been previously divided, epinephrine produces pure acceleration with increase of the auricular, and still more of the ventricular, efficiency (Wiggers, 1916). At the same time, epinephrine has injurious effects on the heart muscle, which may produce ventricular fibrillation and cardiac dilatation if the dosage is excessive or the heart hypersensitive.

Electrocardiograms.—In human subjects, normal or with "irritable hearts," 0.5 mg. of epinephrine, intramuscularly, decreases somewhat the height of the T wave. The conduction time is not altered (Clough, 1919). In *complete heart block,* epinephrine quickens and strengthens the ventricles and auricles (van Egmond, 1913). Clinically, the acceleration occurs without changing the block; it is often interrupted by long pauses with syncope and may be followed by several days of extreme retardation (Lutembacker, 1921).

On perfusion through excised mammalian or cold-blooded hearts, the most conspicuous results of the ordinary experimental dosage consist in marked increase of the rate, excursions and irritability. Existing irregularities are removed, and the effects of muscular depressants are counteracted (aconite, MacNider; strychnine, Januschke, 1910; phenol, chloral and chloroform, Gunn, 1915; potassium, and so forth). A heart which has ceased to beat may often be revived by this drug. If the epinephrine is continued, the stimulation becomes less and may be complicated by depression. There is reason to believe that epinephrine always produces an injurious as well as a stimulant action on the heart, the injurious effect increasing with the concentration, while the stimulation is confined to an intermediate optimal range of concentration; so that the depressant effects predominate for very dilute and for high doses, as also for the prolonged action of intermediate doses (Sollmann and Barlow, 1926).

Excised mammalian heart responds markedly to the epinephrine stimulation. This is utilized in experimental technic to start hearts that have been arrested by injury or asphyxia (Hedbom; perfused apex strips, Leetham, 1913; muscular strips, Taussig and Meserve, 1925). The oxygen metabolism of the heart is increased in proportion to its activity and rate (Evans and Ogawa, 1914). With *excised papillary muscle of cat,* epinephrine causes considerable increase of systolic force; ephedrine may also do so, but the range between stimulant and depressant concentrations is narrow (S. Krop, 1944).

Normal Effects on the Perfused Frog Heart.—Dilutions of 1:10^{13} to 10^9 produce pure depression. Dilutions of 1:10^7 to 10^4 produce powerful stimulation, but this wears off quite rapidly, even when the concentration is kept constant; or rather, it is overcome by the progressive depression. With concentrations above 1:10^6 this gives place promptly to arrhythmia and cardiac arrest. Analogous phenomena are produced in isolated pieces of cardiac muscle; the auricular muscle is more responsive than the ventricular, both as to stimulation and depression. The stimulant concentrations diminish but usually do not remove the Luciani type of irregularity. The lower concentrations increase the irregularity (Sollmann and Barlow, 1926). The refractory phase is not affected (Junkmann, 1925). The *oxygen consumption* of the isolated auricle of frogs is increased by epinephrine (David, 1930).

Antagonisms.—The epinephrine stimulation of the frog heart is mutually antagonistic with the sympathetic depressant ergotoxine (Langecker, 1925; Amsler, 1920), and with the parasympathetic stimulant muscarine (Gottlieb) and acetylcholine (Barlow and Sollmann, 1926). The dioxane F 933 has little effect on the response of the frog and cat heart to epinephrine or sympathetci stimulation (W. T. Hill and Myers, 1939). The depressant action of epinephrine may be additive to the acetylcholine inhibition. A similar additive depression may occur with nicotine and ergotoxine (Amsler, 1920). The epinephrine acceleration is hindered by excess or absence of *calcium,* while potassium has relatively little influence (Libbrecht, 1920). The absence of calcium tends to render epinephrine depressant (Burridge, 1914). *Carbon dioxide* increases the response to epinephrine, although it is depressant when used alone (Patterson, 1916). *Serum* gives a potentiated stimulation with epinephrine (Moog, 1914).

The *tortoise heart* behaves essentially like the frog heart. With auricular segments, epinephrine strengthens the rhythmic contractions and abolishes the tonus waves (Gruber and Markel, 1918). The accelerative effect is greater on sinus segments than on ventricular segment , and it is greater on the apex than on the base of the ventricle. Concentrations higher than 1:10^7 depress the auricular tonus waves (Sollmann and Rossides, 1927). Epinephrine antagonizes the stimulant effect of nicotine and digitalis on the tonus waves, and it partially antagonizes barium (Gruber, 1921).

In birds, the cardiac effects of epinephrine, pituitrine and barium differ considerably from those in mammals (Paton and Watson, 1912). *Embryonal nerve-free chick heart* reacts to epinephrine essentially like the adult heart (Matsumori, 1929).

The *cardiac slowing* which occurs during the epinephrine rise of blood pressure is due practically entirely to reflex stimulation from the carotid sinus and aortic arch by the high pressure, for it does not occur if the nerves from the sinus and the depressor nerves are divided (Heymans and Renouchamps, 1922; W. T. Allen, 1931), or if the rise of pressure is prevented by a compensating device (Brooks *et al.,* 1918). It is mediated through the vagi, and does not occur if these are divided, or paralyzed by atropine. The degree of slowing varies much in different individuals, but it always tends to lessen the rise of pressure, and this mounts much higher if the vagi are cut.

Ventricular extrasystoles are commonly responsible for the cardiac irregularities which may occur apart from the rise of pressure and after denervation of the carotid sinus and after atropine (Terry and Peters, 1933; W. F. Allen, 1934). They are more common after morphine (Heinekamp, 1919) and after chloroform, and are due to direct cardiac injury. The carotid sinus reflex also depresses *the vasomotor and the respiratory center* (Heymans *et al.,* 1933).

Response to Stimulation of the Cardiac Nerves.—With perfused frog hearts, stimulant doses of epinephrine lower the threshold of cardiac vagus stimulation; the response to stimulation of the accelerator is diminished or abolished, since the heart can not go much beyond the augmentation produced by epinephrine (Barlow and Sollmann, 1926). With intact mammals, large doses of epinephrine abolish the vagus response (Kuroda and Kuno, 1915); perhaps because the accelerator response is too strong; or, more probably, because these large doses produce idioventricular rhythm (Winterberg).

Normal Epinephrine Output and Cardiac Activity.—Stewart and Rogoff, 1919, found that temporary exclusion of the adrenal blood from the circulation sometimes influenced the heart, especially when irregularities were present; and that in these cases, the disturbances disappeared when the adrenal blood was readmitted, or if corresponding doses of epinephrine were injected. Cannon, 1921, reported that the *denervated* heart is quickened by stimulation of the adrenals (also by stimulation of the cervical sympathetic and by massage of the thyroid).

Therapeutic Use of Cardiac Stimulation.—This is utilized especially in acute arrest of the previously healthy heart, as in anesthetic accidents or asphyxia, especially of the newborn. Epinephrine may resuscitate hearts that have apparently stopped, although the chance of revival diminishes rapidly, and permanent success is scarcely possible if the circulation has stopped longer than ten or fifteen minutes (Stewart, Guthrie and Pike; Timofecoski and Gofshtadt, 1926). If the collapse is merely threatened, the epinephrine ($\frac{1}{50}$ to $\frac{1}{10}$ mg.) may be injected into the jugular vein or carotid artery (toward the heart), and repeated at intervals. If the pulse can not be felt, $\frac{1}{2}$ to 1 mg. ($\frac{1}{2}$ to 1 cc. of 1:1000) is injected slowly, directly in the heart (right ventricle) by a long fine needle, thrust through the fourth intercostal space, close to the sternum. This heroic procedure would be justified only in otherwise hopeless cases; but it is sometimes successful when joined with artificial respiration and cardiac massage. Strophanthin, 1 mg., has sometimes been added, but may do permanent harm to the myocardium (Gunn and Martin, 1915; Volkmann, 1918).

Intracardiac injection of epinephrine alone has no value unless it is supplemented by cardiac massage. Epinephrine raises the threshold of ventricular fibrillation for a short time (Wégria and Nickerson, 1942), but excessive doses may evoke fatal fibrillation. This risk should be minimized, if feasible, by topical application of 10 per cent metycaine or 5 per cent procaine.

In an instance when the heart resumed thirty-five minutes after it had been arrested, the circulation and respiration remained good for three hours, but decerebrate convulsions set in and terminated in death (R. F. Barber and Madden, 1944).

Injection into the myocardium is more effective than into the cavities of the arrested heart (Sharpey-Schaefer and Bain, 1932); but drugs act from the right auricle even after occlusion of the coronary vessels, presumably by the Thebesian veins (Wiggers, 1930; de Chatel, 1935). Epinephrine accelerates recovery from *ventricular fibrillation* in cats (D. C. Smith and Mulder, 1936). *Reflex arrest of the heart* by pressure on the right carotid sinus is prevented by sympathomimetic drugs. Ephedrine is effective by mouth (Nathanson, 1937).

Against *persistent cardiac weakness*, epinephrine is useless, since its action is too fleeting; and it is dangerous, because the weakened and unstable heart muscle is especially susceptible to the direct injurious effects of the epinephrine and to the high blood pressure it produces.

Traumatic Shock.—Epinephrine may aid temporarily in tiding the patient over hemorrhagic shock, by diverting a large proportion of the blood stream to the coronary and cerebral vessels; but it would need to be promptly supplemented by transfusion (Rous and Wilson, 1918). The epinephrine would be given intravenously, very slowly, carefully watching the pulse; 0.1 mg. has produced alarming symptoms. In *shock proper*, epinephrine is essentially useless, partially because it does not remedy the chief difficulty, *i. e.*, the persistent loss of capillary tone, and partly because its action on the arterioles can not be maintained sufficiently long. This inefficiency is confirmed experimentally in anaphylactic and peptone shock (Simonds, 1916) and in standarized shock produced by controlled bleeding. The benefits of various vasopressor drugs are questionable at best, and do not justify the risk of myocardial damage (D. F. Opdyke, 1944). The pressor response to epinephrine is materially decreased by excessive and deficient pulmonary ventilation, hemorrhage, histamine, and various procedures tending to shock (G. W. Stavraky, 1942).

Epinephrine in Internal Hemorrhage.—Injection of epinephrine into the circulation may sometimes control hemorrhage from inaccessible situations (Hanzlik, 1918); but it is often unsuccessful and may be harmful, for the rise in blood pressure is likely to overcome the local constriction, especially in vessels that react poorly to epinephrine, such as the pulmonary and cerebral. Pulmonary hemorrhage is definitely increased (E. Frey, 1909).

In *intestinal hemorrhage*, the results of Wiggers, 1909, were somewhat more promising: after a momentary increase, the hemorrhage was reduced, and this effect outlasted the rise of pressure. However, Hoskins and Gunning, 1917, found that small doses generally dilate the intestinal vessels (increased volume and vein outflow). G. A. Hartman and McPhedran, 1917, also confirm this, but claim that still smaller doses constrict the vessels of the intestines, kidney and generally also those of the spleen.

The **coagulability of the blood** is not affected by direct addition of epinephrine, but when this is injected into an animal, coagulation time is shortened by small doses (0.002 mg. per Kg.) and retarded by large doses (0.05 mg.) (Cannon and Mendenhall, 1914). If the abdominal organs are removed from the circulation, these effects do not occur, so that the epinephrine acts presumably on the liver cells. Grabfield, 1916, found that the increased coagulability with small doses is due to increased prothrombin.

Hemolytic Action.—Epinephrine is strongly hemolytic for beef blood and to a less degree for other animals. It also produces methemoglobin. Serum weakens the action (Kariga and Tanaka, 1913).

Blood Volume and Cell Count.—Intravenous injection of fairly large doses of epinephrine generally causes a small decrease of plasma volume, estimated by dye methods, but this is variable (Gregersen and Pinkston, 1936), or may be absent (Yang and Chang, 1930). There is always an increase of the red and white cell count (Lamson and Keith, 1916) and of the total circulating erythrocytes (CO method, Hitzenberger and Tuchfeld, 1929). The blood platelets are also rapidly mobilized (Behamou and Nouchy, 1930), and the reticulocyte count rises (in young rabbits; Istamanowa and Chudoroschewa, 1910). Pituitary injection, physostigmine, strychnine and stimulation on the sciatic nerve produce similar effects (Edmunds and Lloyd, 1923), while histamine decreases the erythrocytes and increases plasma volume. The epinephrine polycythemia is attributed chiefly to mobilization of cells of the splenic pulp by contraction of the spleen (Edmunds and Stone, 1924; E. E. Nelson, 1924; Yang and Chang, 1930). This may be of some benefit in shock and hemorrhage, and especially in CO poisoning and methemoglobinemia.

Considerable increase occurs after removal of the spleen, so that about half of the cells are mobilized from other organs (P. F. Hahn, Bale and Bonner, 1943, "tagged" erythrocytes in pentobarbital anesthesia). Daily administration of epinephrine or posterior pituitary extract to splenectomized rabbits also produces polycythemia, attributed to increased erythropoiesis by vasoconstrictor ischemia of the bone marrow (J. E. Davis, 1942).

Leukocytes.—In dogs, the leukocytosis is followed by leukopenia, due to retention and destruction of the leukocytes in the liver (Fegler, 1927).

Normal Spleen.—Hoskins and Gunning, 1917, found that effective doses, in intact animals, cause a brief dilatation, followed by contraction. The threshold is more sensitive than that for the general arterial pressure. Rhythmic contractions of the spleen are sometimes started. In *malarial patients* with chronic enlargement of the spleen hypodermic injection of epinephrine, 0.25 to 1 cc. of 1:1000 rarely causes reappearance of a few parasites in the blood, never enough to provoke a febrile attack (Morishita and Furutama, 1927); the red cells are generally not increased, but there is always some leukocytosis, especially of the monocytes and large lymphocytes (Hughes and Shrivastava, 1930). Riolo, 1935, reported marked reduction of the spleen tumor from twenty to thirty daily injections intravenously, increasing from $\frac{1}{100}$ to $\frac{1}{10}$ mg.

The Toxic Effects of Epinephrine.—The *major accidents*, acute cardiac dilatation, pulmonary edema, ventricular fibrillation, terminating in death, usually follow intravenous injection and are especially liable to occur if the heart is already weakened or overexcitable, in cardiac disease, or as the result of chloroform, cyclopropane or other cardiac poisons. The induction period of chloroform anesthesia is especially dangerous. Such accidents should be treated with artificial respiration.

Gormsen, 1939, reviews twenty-eight *deaths from hypodermic injection of epinephrine*, reported in the literature, all due to overdosage by error in the concentration of the solution. The minimal fatal dose hypodermically is about 10 mg. The symptoms are immediate pain in the neck, anxiety, pallor, vomiting, dyspnea, rapid pulse, high blood pressure, collapse, death often in a few minutes. Necropsy shows edema and extensive hemorrhages in the lungs and small interstitial hemorrhages in the kidneys. In *cardiac insufficiency*, the hypodermic injection of 1 mg. generally produces distinct dilatation and extrasystoles (M. Loper *et al.*, 1918; D. Roth, 1914). Fatalities have occurred from 0.4 mg. hypodermically (Fridericia, 1915). In *poisoning by cardiac depressants* (*f. i.*, chloroform, phenol or caffeine) the intravenous injection of epinephrine temporarily restores the blood pressure, and this may give the heart a chance to recover. But if the blood pressure is raised much above the normal, the heart may go into ventricular fibrillation, and this may occur from doses of epinephrine which would be quite safe in healthy individuals (*chloroform*, Nobel and Rothberger, 1914; *phenol*, Sollmann). It is probably due to abrupt upset of the autonomic equilibrium, and it may be prevented by section of the carotid sinus and depressor nerves, or by preliminary injection of pilocarpine (Bardier and Stillmunker, 1927), or of epinephrine itself when this is administered previous to the chloroform. Ventricular fibrillation in response to benzene and epinephrine is a fairly satisfactory means of testing the susceptibility of the heart to fibrillation ("benzol-adrenalin" test; Wégria and Nickerson, 1943).

Epinephrine pulmonary edema is not due to back pressure as such, for it occurs only if hydremic plethora exists or if marked cardiac irregularity occurs. It is seen more often if the vagi have been divided or if asphyxia is present; conversely, artificial respiration tends to prevent the occurrence of the edema (Gates and Auer, 1917).

Fatal Effects in Animals.—Excessive doses of epinephrine produce vomiting, excitement, debility, bloody diarrhea, hematuria, ascending central paralysis, great fall of temperature, occasionally convulsions, complete prostration and *death* by respiratory (cat) or cardiac (dog) paralysis. Rabbits show multiple pulmonary hemorrhages, probably associated with edema. The *fatal dose* varies considerably (usually 0.1 to 0.6 mg. per kilogram intravenously, or 2.5 to 10 mg. per kilogram hypodermically), but is about five hundred times the therapeutic dose. A noticeable rise of blood pressure can be seen after $\frac{1}{1800}$ of the fatal dose. *Guanine* is said to lessen the toxicity and glycosuria. Atropine is also claimed to decrease the toxicity (Leo Schmidt, 1919). The toxic effects are the result of the peripheral actions; for as Cushny, 1909, pointed out, the ratio of activity of the different isomers is the same for the toxic as for the blood pressure effects. *Oral administration in rabbits* produces hyperglycemia and polyuria or oliguria, according to the dose. Large doses are followed by death in one and a half or two days, through damage to the stomach and intestines, the ischemia causing necrosis and perforation (S. Rosenkranz, 1938).

Minor Accidents; Hypersusceptibility.—The local application or hypodermic injection of epinephrine in ordinary doses does not normally produce marked symptoms. Not infrequently, however, excitable or susceptible patients respond in a few minutes by pallor, tremors, anxiety and nervousness, tachycardia and palpitation, precordial distress, increased rate of respiration, rise of blood pressure and temperature, wakefulness and sometimes hyperglycemia (Hewlett, 1918). The symptoms may be alarming. They usually pass away in a short time, but they may be fatal (Fischer, 1920). This hypersusceptibility occurs especially in patients of nervous temperament, most markedly in those with toxic goiters (also in experimental hyperthyroidism in rabbits; H. Rosenblum *et al.*, 1933); also in hypertension (O'Hare, 1920). It has been used (½ mg., intramuscularly) as a test for neurasthenia and "irritable heart" (D. M. Lyon, 1924). Serious results have followed epinephrine injection in angina pectoris (Cottrell and Wood, 1931).

Epinephrine Atheroma.—If rabbits receive frequent injections of large doses of epinephrine, atheromatous changes and calcareous patches are often observed in the aorta and other large vessels (d'Amato, 1905). These degenerations are not seen in dogs (Pearce and Stanton, 1906), or in monkeys, and presumably not in man. Dogs also give negative results with nicotine, lead or toxins (Adler, 1914). Identical lesions often occur spontaneously in rabbits which have never received epinephrine. The frequency of these spontaneous lesions varies in different series from 3 to 30 per cent, but they are so markedly more frequent after epinephrine treatment that this must at least exaggerate the tendency to the degeneration (I. Levin and Larkin, 1910). Success depends on frequent repetition of the epinephrine rather than on the size of the dose (Fleisher, 1909). The injury has been attributed to high blood pressure and to direct toxicity by epinephrine. The older experiments undertaken to decide between these views (summarized by I. Adler, 1908) did not take account of the spontaneous occurrence of the lesions. The toxic theory seems the more probable; although Dixon, 1913, stated that all pressor agencies, when repeatedly applied, produce degenerations of the middle coat. It is highly doubtful whether these atheromas of rabbits have any relation to human atheroma. Atheroma is also produced by feeding cholesterol, cottonseed oil, the aldehydes of fatty acids, hydrochloric acid, and by paracresol (Denny and Frothingham, 1914). The high blood pressure of *clinical hypertension* is definitely not due to epinephrine, for epinephrine would cause other marked disturbances, for instance of peristalsis, in doses much smaller than are required materially to raise the blood pressure.

Epinephrine Myocarditis.—Rabbits often show chronic myo-, endo- and pericarditis, after repeated epinephrine injections. This lesion, which is apparently independent of the atheroma, is much more frequent (60 per cent) if a single intravenous injection of epinephrine (0.2 mg.) is combined with sparteine (12 mg.), caffeine (25 mg.) or strophanthin (these drugs never cause the lesion if they are used without the epinephrine). The changes in the heart muscle start at once, progress for some seven days, persist about six weeks and then retrogress completely by sixteen weeks (Christian and Walker, 1911). Fleisher and Loeb, 1910, attribute the lesions to mechanical strain from excessive contraction of the muscle fibers, for the lesions are situated mainly at the base of the left ventricle, where the strain is greatest. The changes are analogous to those shown by striated muscle subjected to overexertion; and the lesions do not appear in the relatively stronger and more resistant hearts of dogs. H. A. Stewart, 1912, prefers a toxic theory. Hearts which show the microscopic changes are physiologically inferior to the normal; they are less able to cope with extra demands; and the animals appear more disposed to edemas (uranium) and to bacterial infections.

Respiration.—The epinephrine rise of blood pressure is generally accompanied by decrease of the rate and depth of respiration, sometimes to apnea. This was attributed to presso-receptor reflexes from the carotid sinus and aortic regions (Heymans *et al.*, 1933), but is probably due to reduced activity of the chemo-receptors (Gernandt *et al.*, 1945). It is followed by more lasting stimulation (C. F. Schmidt, 1929). *Central action currents* appear on intravenous injection (B. I. Hasama, 1935). In man, 1 mg. hypodermically increases the respiration volume by 8 to 94, mean 50 per cent; the rate is unchanged or also increased (Fuchs and Roth, 1912). Voegtlin and Wiggers, 1918, tried epinephrine against narcotic depression of the respiration, with doubtful results. Schmidt found it more encouraging, but it is inferior to ephedrine.

Bronchioles are dilated by epinephrine. It antagonizes all types of constrictor agents (choline esters, pilocarpine, histamine, barium anaphylaxis, and so forth), and is additive with dilator agents (atropine, nitrites).

The bronchodilatation was confirmed in intact animals by Januschke and Pollak, 1911, and others; on excised tracheal muscle by Trendelenburg, 1912; and on microscopic sections by Sollmann and Gilbert, 1937. It is more marked if the bronchial tone is high (Golla and Symes, 1913 and later). It is not prevented by ergotoxine or ergotamine, but is hindered by F 933 (Melville, 1937). Epinephrine and epinine are the most potent dilators of the group; arterenol is good; neosynephrine is fair, and ephedrine and benzedrine are poor (Cameron and Tainter, 1936)

Relief of Spasmodic Asthma, Anaphylactic Reactions, Serum Disease, Nitritoid Crises of Arsphenamine, Angioneurotic Edema, Urticaria, and the Like.—Epinephrine relieves these promptly (Kaplan, 1905), and is the most effective agent against them, although it is not always completely successful. The mechanism by which it checks edema formation is not understood. Clinically, 0.1 to 0.5 cc. of the 1:1000 solution is injected intramuscularly, repeated in half an hour if necessary and if there are no marked side effects (anxiety, tremor, tachycardia), It is more effective if given early, as preventive if possible. Atropine, 0.6 mg., may be added. Intramuscular injection of *oil suspension* (2 mg. of the powdered base in 1 cc. of peanut oil) gives more lasting action and is more economical in chronic bronchial asthma (Keeney *et al.*, 1939); but it may exceptionally produce prompt and severe toxic epinephrine reactions (Dorwart, 1940). Graeser and Rowe, 1936, advocate *inhalation* of a nebulized spray of 1:100 solution, especially for children, as equally effective for relieving asthma, but in severe cases it does not penetrate far enough into the bronchial tree (Graeser, 1939). This has also been used against angioneurotic edema (Klinefelder, 1937). *Ephedrine* can be administered by mouth, but it is less effective in asthma and is used chiefly in hay fever. Both agents may be applied locally against turgor of the turbinates or congestive closure of the nasal sinuses.

A patient taking ten deep *inhalations* of the nebulized 1 per cent epinephrine solution receives less than 0.08 mg. of epinephrine into the mouth, and only a hundredth of this reaches the bronchioles, much less than would be needed for systemic effects. The action is therefore purely local, but prolonged inhalation causes dangerous intoxication. Frequent repetition causes tracheal irritation, epithelial desquamation and inflammatory changes (Gagliani *et al.*, 1939).

Edemic Reactions.—Epinephrine diminishes the wheal reaction of the skin by codeine, which is allied to the edemic reactions of anaphylaxis. This response is apparently secured only by systemic and not by local administration (Pilcher, 1925), so that it can not be due to vasoconstriction. It is similarly effective against dionin chemosis and against paraphenylendiamine edema; ephedrine, tyramine and pituitary solution are much less effective (Tainter, 1928).

Eye.—Epinephrine has a mydriatic effect. This occurs readily in frogs; but only under specially favorable conditions in mammals. In the *normal human eye*, local instillation of 2 per cent epinephrine usually dilates it somewhat within an hour (S. C. Howell, 1934), but much less than with ephedrine. An unpleasant sensation of muscle spasm results from 1:1000 instillation, so that it should not be used (Fantus).

Epinephrine mydriasis in mammals may be produced by large intravenous doses. With local application, the mydriatic effect may be obtained if the oculomotor tone is low (weak illumination, W. H. Schultz, 1908), if the absorption is hastened (conjunctivitis, H. Straub, 1919), or if the excitability of the sympathetic is increased. This is supposed to occur in Basedow's disease and in pancreatic insufficiency. O. Loewi, 1908, accordingly proposed a mydriatic response to epinephrine as a diagnostic sign in these diseases, but later work showed that the increased mydriatic reaction occurs in all types of hyperglycemia (A. Loewy and Rosenberg, 1914). The sensitiveness also appears somewhat increased in chronic nephritis (Kato and Watanabe, 1920).

Denervation.—The mydriatic response to epinephrine is obtained a few days after excision of the superior cervical ganglion (Meltzer and Auer, 1904), or after removal of the ciliary ganglion (Joseph, 1915). This may be attributed to increased excitability of the sympathetic distribution, accompanying the degenerative changes which follow the excision (T. Schlossberg, 1932). An analogous increase of excitability in degenerating structures to epinephrine occurs in the ear vessels (Meltzer and Auer, 1903) and in other organs (Elliott, 1905); also in skeletal muscle on degeneration of the sciatic nerve (Edmunds and Roth, 1909). G. N. Stewart, Rogoff and Gibson, 1916, found the mydriatic responses of the denervated pupil a sensitive and reliable test for the discharge of epinephrine.

Localization of Mydriatic Action.—Lewandowsky, 1898, showed that the mydriatic effect occurs after degeneration of the sympathetic, so that the action must be on the receptive mechanism. The excised sphincter of the mammalian iris is also relaxed by epinephrine. This is counteracted by physostigmine, with mutual antagonism (Joseph, 1917). Pituitary counteracts the mydriasis in intact animals (Githens and Meltzer, 1917).

Other Evidences of Ocular Sympathetic Stimulation.—The mydriasis is accompanied by separation of the lids, protrusion of the eyeball and withdrawal of the nictitating membrane.

Mydriatic Reaction in Frogs.—Frogs are especially susceptible to the mydriatic action; and this may be produced by systemic application (1 cc., 1:100,000, into lymph sac) as well as in the enucleated eye (1:5000; Meltzer, 1909). The dilatation is prompt and persistent, submaximal, indifferent to light.

Epinephrine Miosis.—After repeated injections or local instillations, epinephrine may produce constriction of the pupils in mammals. This altered response is attributed to a change in the pupillo-dilator muscle (Kato and Watanabe, 1920).

Intra-Ocular Pressure.—The effects vary, but normal pressures are generally lowered somewhat by local application of 2 per cent solution of epinephrine (Howell, 1934), or by subconjunctival injection of 0.2 to 0.5 cc. of 1:1000 solution. In glaucoma with pressures above 40 mm. Hg., epinephrine injection causes no change (Vannas, 1927). The fall is probably due to intra-ocular vasoconstriction.

Intra-ocular injection of epinephrine into rabbits produces intense contraction of the retinal arteries, paleness of the disc and the ophthalmoscopic picture of optic atrophy. These effects persist for weeks or months and are not overcome by nitrite, atropine, pilocarpine or dionin. Albino rabbits developed cataract. These fundus changes did not occur in cats (Redslob, 1929). With intravenous injection, the rise of general arterial blood pressure tends to break down the capillary resistance, and so to raise the intra-ocular pressure. All doses contract the smooth muscle of the orbit, which raises the intra-ocular pressure. Mydriasis does not play a significant role (Duke-Elder *et al.*, 1932).

Lens opacities may be induced in mice and rats by epinephrine; a single peritoneal injection of 5 to 10 mg. per Kg. may suffice. The opacities are subcapsular and transitory and appear to be related to derangement of carbohydrate metabolism and circulatory impairment, resulting in increase of nonglucose-reducing substances in the blood. The liability is increased by inducing shock with histamine, potassium poisoning and adrenal cortex deficiency; it is decreased by ergotamine or phlorhizin (C. Suden, 1940).

Effect on Secretions.—Epinephrine may provoke secretion of the salivary and lacrimal glands (Langley, 1901); and of the skin glands of frogs (Ehrmann, 1905). The increased secretion of the submaxillary glands is accompanied by increased blood flow (Solem and Lommen, 1915). It occurs after degeneration of the chorda tympani nerve (Bonvallet and Minz, 1938). Small vasodilator doses (0.01 mg. for cats) increase the secretory response to *cholinergic drugs;* 0.05 mg. causes vasoconstriction and diminished secretory response (G. W. Stavraky, 1942). In most glands, however, secretion is diminished or arrested through the vasoconstriction. This is notably so with *pancreatic secretion* (Edmunds, 1909). This is apparently due to diminished blood supply, for the volume of the pancreas is decreased even by small doses and independently of the general blood pressure (Mann and McLachlin, 1917). Downs and Eddy, 1919, claim that *bile secretion* is increased by epinephrine. *Sweat* is increased in animals (Muto, 1916. He finds that the sweat glands are innervated by both the sympathetic and parasympathetic.). The sympathetic predominates in horse and sheep; whereas man, cattle and cats are more subject to the parasympathetic. Injection of epinephrine into a cat's paw produces sweating when the sciatic or posterior nerve roots have been divided. Injection at a distance or intravenously was ineffective (Dieden, 1916).

Gastric motility is depressed by epinephrine. The pyloric sphincter relaxes if the gastric tonus was normal or high; if it was low it is generally raised by epinephrine (J. E. Thomas, 1929). Similar depressive effects are produced by ephedrine and by both the vasopressor and the oxytocic fractions of pituitary (Schroder, 1933). *Excised stomach* is relaxed in most mammals, but contracted in some. The gastric sphincters are always contracted (Thomas, 1929).

Intestinal Motility.—Epinephrine relaxes the tonus and inhibits peristalsis in excised intestines, as also in fistula segments of unanesthetized animals. The sensitivity of excised intestines to epinephrine is less in rabbits than in cats and guinea pigs (Achutin, 1933). Atropine prevents and reverses the relaxing action in dogs (Raymond-Hamet, 1934). Similar effects are produced by ephedrine and tyramine, but these are antagonized by cocaine, which does not antagonize this action of epinephrine (Gruber, 1936). Epinephrine inhibition of excised intestine is antagonized reversibly by lack of oxygen (E. Starkenstein, 1941).

Very dilute solutions of epinephrine increase intestinal contractions in mammals (Hoskins, 1912) and in frogs (Roth).

The *ileocolic sphincter* differs from the ordinary intestine, being contracted by epinephrine or splanchnic stimulation (Elliot, 1904).

The gallbladder is relaxed by epinephrine (Lieb and McWhorter, 1915).

The **uterine responses** differ with conditions. *Clinically*, intramuscular injection of epinephrine, ½ cc. of 1:1000, produces prompt but brief relaxation of the parturient uterus, even if pitocin or ergotamine has been administered. This may be used to facilitate operative manipulation (Dodek, 1932; Bourne and Burn, 1927; Daro *et al.*, 1940).

Others, however, report divergent results for human uterus. W. E. Brown and Wilder, 1943, recording postpartum contractions by intra-uterine bag, report that intramuscular or intravenous epinephrine produces premature contraction followed by a compensating pause, but no inhibition or relaxation. J. Daels, 1941, finds on excised human gravid and nongravid uterus that epinephrine stimulates the exterior, propulsive muscular layer,

and inhibits the interior and cervical layer. This probably explains the contradictions; both actions would assist parturition.

The *effects in animals* correspond to stimulation of the hypogastric nerve: in pregnant cats it produces contraction; in nonpregnant cats, relaxation (Cushny, Kehrer, Dale); in nonpregnant guinea pigs, relaxation; in dogs, contraction followed by relaxation; in rabbits, increased tonus (Biagi, 1905). The fallopian tubes are also stimulated to contraction (Gunn, 1914). Through an artificial abdominal wall of celluloid, Ludwig and Lenz, 1923, observed that epinephrine arouses peristalsis in the uterus of the gravid rabbit or cat; but in the nongravid and puerperal animals it produces prompt arrest and fixation of the uterus in whatever tonus prevails at the moment. In the final stages of pregnancy the cat uterus is again inhibited by epinephrine and by hypogastric nerve stimulation (E. C. Del Pozo, 1946).

Modification by Sex Hormones.—The excised uterus of virgin or spayed guinea pigs, which is normally relaxed by epinephrine, is stimulated in about half of such animals if they have been treated with estrogen. If they received progesterone together with the estrogen, epinephrine is not stimulant until the uterus has been kept in warm Locke solution for two or three hours. Ergotoxin abolishes all augmentory epinephrine response (G. Balassa, 1941).

Reversal of Epinephrine Inhibition by Pituitary Extract.—The uteri of guinea pigs and nonpregnant cats are ordinarily relaxed by epinephrine. If, however, they are first treated with pituitary solution, the epinephrine produces contraction. This sensitizing action seems to be in the peripheral nervous mechanism and not in the muscle itself (Cow, 1919).

Excised Ureter.—Epinephrine (1:500,000) increases the rate and tonus, or starts the contractions. The effect is reversed by ergotoxine (Macht, 1916; Gruber, 1930). The response of the epinephrine isomers differs only quantitatively, the levo being much more stimulant than the dextro (Macht, 1918). The *urinary bladder* was discussed in the general section on Autonomic Poisons.

The smooth muscle of the **amnion** of birds, which is completely devoid of nerves, responds to epinephrine and other autonomic poisons (Baur, 1928).

The **pigment cells** in the frog's skin are contracted into spheres (Lieben, 1906). This also occurs in the melanophores of fishes, the effect being reversed by ergotoxine (Spaeth and Barbour, 1917).

Epinephrine in Annelids.—Chromophile material exists in the ganglia of a number of species, including the earthworms and leech. These have vascular systems, the contractions of which are accelerated by epinephrine (Gaskell, 1919).

The bioluminescence of fireflies (Photuris pennsylvanica) is modified by epinephrine into a steady bright glow, perhaps by direct action on the tracheal end cells (G. A. Emerson and Emerson, 1941).

Protozoa.—The pulsations of the vacuoles of paramecium are accelerated by epinephrine, pituitary and pineal extracts (Feather, 1919).

Skeletal Muscle.—Epinephrine, when applied to excised skeletal muscles, has practically no effect on their contraction, even in concentrations up to 1:15,000 (Kuno, 1915). The injection of epinephrine into living animals increases the efficiency (height of contraction and irritability) of their muscles, the increase persisting after the muscle is excised (Oliver and Schaefer, 1895). A sensation of muscle spasm is noticeable clinically if epinephrine solution, 1:1000, is dropped into the conjunctival sac (Fantus). Intravenous injection of epinephrine momentarily restores decerebrate rigidity that was relaxed by curare (Bremer and Titeca, 1928), but it has no action on normal tonus (Bremer, 1932). The improvement is particularly marked if the muscles (of cats) have been previously fatigued, or weakened by acids (Gruber and Kretschmer, 1918). The increased efficiency is partly an indirect effect, attributable to improved circulation through the muscle while this is still in the body (Gunning, 1917). *Creatine formation* is increased by epinephrine, even after curare (Riesser, 1916).

Nerve trunks are not affected.

Epinephrine Hyperglycemia. — Clinical doses of epinephrine (1 mg. hypodermically) do not alter the blood sugar level in normal human subjects, but they increase the sensitiveness to alimentary glycosuria (Landau, 1914); and in epinephrine-sensitive patients 0.5 mg. intramuscularly causes hyperglycemia (Peabody *et al.*, 1918) and decrease of the reserve alkali of the blood (Peters and Geyelin, 1917). Intravenous injection of epinephrine into rabbits, at the rate of 0.003 to 0.06 mg. per Kg. per hour, increases the level of sugar (F. Blum, 1901) and lactic acid in the blood, without altering the metabolic rate, and without producing the typical sympathomimetic actions. This quantity of epinephrine is considered within the physiological output and is about an eighth of that required to raise the blood pressure (Cori *et al.*, 1930). If the sugar level rises sufficiently, glycosuria results, generally proportional to the hyperglycemia (Gramenitzki, 1912).

The hyperglycemia ceases promptly by the destruction of epinephrine, when the injection is discontinued. A given quantity of epinephrine is more effective when injected slowly or by hypodermic injection than when given as a single intravenous injection (Barbour and Rapoport, 1921). With partial oxidation of epinephrine, the glycosuric action is lost first (McGuigan and Mostrom, 1913).

Mechanism of the Epinephrine Hyperglycemia.—The *initial* rise of blood sugar involves the conversion of hepatic glycogen into sugar, and is analogous to asphyxial glycosuria, diabetic puncture, or stimulation of the hepatic, splanchnic or sensory nerves; all acting probably on sympathetic nerves controlling the glycogenic functions.

The hyperglycemia is *not asphyxial*, for it is not prevented by artificial respiration; *nor is it renal*, for it occurs after excision of the kidneys (Zuelzer, 1901). It is not checked by barbiturates, and is probably due to a peripheral action (D. Campbell and Morgan, 1933). On the other hand, epinephrine increases the utilization of dextrose by the tissues (Himsworth and Scott, 1938).

Glycogenolysis as the source of the sugar is indicated by the fact that the degree of hyperglycemia and glycosuria depends upon the glycogen content of the animal; they are more intense in animals rich in glycogen; and conversely there is no glycosuria in animals whose glycogen has been completely removed by phlorhizin; and an existing phlorhizin glycosuria is not increased by epinephrine (Ringer, 1910). The evidence for the hepatic origin of the sugar is also convincing. The blood of the hepatic vein contains more sugar than that of the portal; sugar formation is increased on perfusion of the excised liver, and conversely there is no glycosuria when the functions of the liver have been injured by phosphorus (E. Frank and Isaac, 1911). The muscle glycogen is also mobilized by epinephrine, even after excision of the liver (E. Geiger, 1930). *If the injection of epinephrine is continued for some time*, the liver glycogen again increases, although the blood sugar and lactic acid continue high. The mechanism of this is obscure. Cori *et al.* reported that the muscle glycogen continues to fall and suggested that epinephrine stimulates the production of lactic acid from muscle glycogen and that this is then changed into liver glycogen, and this into sugar; but in fasting rabbits the muscle glycogen may also be increased by epinephrine (Markowitz, 1925), indicating formation of carbohydrate from some other source ("gluconeogenesis"; review, Macleod, 1934).

Habituation.—The hyperglycemic response in rabbits is not materially altered by prolonged daily repetition of hypodermic epinephrine injections (Affleck, 1929), except as the glycogen supply is depleted. Hyperglycemia persists somewhat longer than the glycosuria, so that continued injection of epinephrine appears to decrease the permeability of the kidneys for glucose (Pollak, 1909, 1911), perhaps by vasoconstriction. At this stage, diabetic puncture also produces only hyperglycemia, and not glycosuria. Phlorhizin, however, still causes glycosuria (Biberfeld, 1916).

Interfering Factors.—Epinephrine glycosuria is prevented by ergotoxine (Loewi), which diminishes the hyperglycemia and also the permeability of the kidney for sugar but not for chloride (Miculicich, 1912). It is also prevented by nicotine (Hirayama, 1911), by lymphogogues (peptone, hirudin; Miculicich), and by repeated hemorrhage (Wilenko, 1912). Urethane increases the activity (Underhill, 1911). Antipyretics suppress the glycosuria but not the hyperglycemia, so that their effect must be on renal permeability (Mansfield and Purjesz, 1915). *Amino acids* are reported to influence epinephrine hyperglycemia in different directions: tyrosine and tryptophane as increasing it; leucine and histidine as inhibiting; and phenylalanine, glutamic acid and amino acetic acid as indifferent (Chikano, 1929).

Relation of Adrenals to Other Glycosurias.—Removal of the adrenals prevents the usual glycosuric response to diabetic puncture, theobromine and splanchnic stimulation, probably as a result of shock (Stewart and Rogoff, 1918, 1920).

Related Amines.—The effects of forty amines on blood sugar are reported by R. C. Anderson and Chen, 1934.

Gaseous Metabolism.—The hypodermic injection of 0.5 mg. of epinephrine increases the basal metabolism of human subjects by 15 to 40 per cent. This has no relation to the thyroid activity (Marine and Lenhart, 1920). The respiratory quotient often rises (Tompkins *et al.*, 1919). The mechanism of the increased metabolism is not understood. It is out of proportion to the mobilization of glucose (Boothby and Sandiford, 1920). It does not appear to be due to excitement.

In unanesthetized, trained dogs, epinephrine (20 γ per Kg., intramuscularly) also increases respiratory metabolism, by 20 per cent for two hours (J. de Moerloose, 1942).

In dogs under morphine-barbiturate anesthesia, prolonged injection of small amounts of epinephrine, which have no effect on the heart rate and blood pressure, produces a transient decrease of gas metabolism. Rapid injection causes increase. The respiratory quotient rises in either case (Mertens and Rein, 1938).

Heat Regulation.—Injection of epinephrine produces fever (Freund and Marchand, 1913). Hirsch, 1913, found, presumably under different conditions, that the injection of epinephrine or pancreas lowers temperature by decreasing heat production. Cloetta and Waser, 1915, described rise of brain temperature and cooling of skin, with 0.2 mg. in rabbits, intravenously. Intracerebral injection acted similarly. The rise was not prevented by ergotoxine.

Nitrogen Metabolism.—Epinephrine, by vein or hypodermically, has little or no influence on the nitrogen excretion (Lusk, 1914). In dogs, large doses, hypodermically, increase the excretion of uric acid and especially of allantoin (Falta, 1914). Addis *et al.*, 1918, believe that the hypodermic injection of epinephrine into rabbits increases the *urea* excretion capacity. Maximal doses, however, diminish the output. The effect is smaller if the urea concentration of the blood is high.

Potassium Level of Blood Serum.—Intravenous injection of 0.05 to 0.2 mg. of epinephrine into dogs, cats or rabbits promptly increases the K level to 40 per cent above the normal, parallel to the hyperglycemia. The potassium is probably mobilized from the liver, for the rise is prevented by removal of the liver, and also by ergotamine or curare. In man, 0.1 mg. of epinephrine causes immediate and marked fall of the K level. The Na level is unchanged (A. Keys, 1938; D'Silva, 1934, 1936).

The **urinary phosphate excretion** is reported to be diminished by epinephrine (also by insulin).

Normal Distribution of Epinephrine.—The principal depot of epinephrine is in the medulla of the adrenal gland, in its "chromaffin" cells which are intermingled with nervous structures. It occurs also in special cells in other situations, always closely associated with sympathetic ganglia (Elliott, 1905). The neurohormone theory of sympathetic stimulation postulates that it or a near derivative is universally present, as "sympathin" about the terminations of the sympathetic nerves, although the quantity there is too small to be demonstrated chemically. It is not known whether this "sympathin" is formed locally or supplied by the suprarenal medulla; but the epinephrine in the circulation comes chiefly from the latter source. The level of epinephrine in the blood, however, is not enough even under the most favorable conditions to exert any effect on blood pressure, or even on the much more sensitive intestine, although it can be demonstrated in the blood of the adrenal vein by the blood pressure and by the pupil test (Stewart and Rogoff, 1916) or by the denervated heart (Cannon). It may therefore be doubted whether the adrenal output of epinephrine has much physiologic significance. It is even conceivable that adrenal epinephrine is mainly a waste product temporarily stored and perhaps destroyed in these glands; but it appears more probable that they constitute a depot which helps to maintain the normal epinephrine concentration of the sympathetic terminals. Adrenal epinephrine secretion is certainly not essential to life, for animals, including monkeys, live without noticeable disturbance when their output of epinephrine has been practically suppressed by excision of one adrenal, and section of the nerves of the other (Stewart and Rogoff, 1917, 1919). Cannon (review, 1940) believes that the adrenal medulla has some importance as an adjuvant to sympathetic impulses, in the extra demands of vigorous muscular work, asphyxia, low blood pressure, chilling and hypoglycemia. Epinephrine is not concerned in clinical hypertension, nor has the causation of any other pathologic condition been definitely connected with altered epinephrine content of the blood.

The *formation of epinephrine in the adrenal medulla* appears to be rapid, for if the store of epinephrine has been depleted to a third of the normal by the physostigmine, it is practically restored to the normal amount within twenty-four hours (C. W. Edmunds and Smith 1931).

The *total amount of epinephrine in the suprarenal glands* in man is normally about 4 to 5 mg. per gland (Elliott, 1914); in dogs, 2 mg.; in cats, 0.19 mg. (Marchetti, 1915); in sheep, to 7 mg. (Folin, Cannon and Denis, 1913). The percentage is about 0.1 per cent of the moist weight, in all animals. The content does not vary with the seasons (Seidell and Fenger, 1914). In glands obtained from autopsy material from various diseases, the epinephrine content is generally somewhat low, about 0.35 per cent of the dry weight in place of the normal 0.4 per cent (Lucksch, 1917). Epinephrine is present early in *fetal animals* (McCord, 1915). In the human fetus, it is absent at six months, but present at full term (J. H. Lewis, 1916).

Normal Adrenal Output and Concentration in Blood.—Epinephrine can be demonstrated in the blood of the adrenal veins; under special conditions and by especially sensitive methods also in the vena cava. The normal adrenal output in the cat and dog is about 0.00025 mg. per kilogram of body weight (Stewart and Rogoff, 1917, 1923). The normal concentration in the circulating blood is not known, but it has been deduced as 1:2 times 10^9, or 1 mg. in 2000 liters (Stewart, Mellon Lecture, 1926).

The *splanchnic control of the epinephrine output from the suprarenal medulla* seems to be complete in the sense that epinephrine disappears from the adrenal vein blood if the splanchnic nerves are divided, and stimulation of the peripheral stump of the divided splanchnic nerves increases the epinephrine output up to twenty times the normal, sufficiently to raise the blood pressure (Stewart and Rogoff, 1916).

Role of Epinephrine in Splanchnic Pressor Response.—A part of the blood pressure changes on splanchnic stimulation is due to the discharge of epinephrine (Perlman and Vincent, 1919). The phenomena are affected by the anesthetic (Parsons and Vincent, 1917) and are sometimes abolished by caffeine, curare and morphine (Perlman and Vincent).

Spinal Center.—In cats, epinephrine is liberated after section of the cord as low as the last cervical, but not after section of the mid-dorsal region (Stewart and Rogoff, 1917).

Drugs on the Adrenal Epinephrine Output.—This is increased by toxic doses of strychnine (up to one hundred times), and by morphine, acetylcholine, pilocarpine and physostigmine (the latter may deplete the normal epinephrine store of the glands to an eighth of the normal; Edmunds and Smith, 1931). Nicotine causes a temporary increase, followed in less than a minute by marked decrease.

The adrenal medulla is innervated by *cholinergic preganglionic sympathetic fibers*, as are also other sympathetic ganglia (Feldberg and Vartianinen, 1934). Physostigmine and neostigmine potentiate the action of coline esters both on sympathetic ganglia and adrenal medulla (W. B. Cannon and Rosenblueth, 1937).

The *acetylcholine* increase of epinephrine output is further increased by atropine (Houssay and Molinelli). Their actions are peripheral (H. Hermann *et al.*, 1937). *Atropine* has no effect in itself, but large doses diminish considerably the amount of epinephrine secreted in response to splanchnic stimulation, but not to nicotine or quaternary ammonium bases (J. T. Lewis and Luduena, 1934). *Potassium salts* increase (Hazard, 1933) by direct peripheral action, presumably through acetylcholine (H. Hermann *et al.*, 1938). *Physostigmine* potentiates acetylcholine, nicotine, hordenine and lobeline (J. Lévy and Olszycka, 1937). Curare decreases; strophanthin and anesthetics have no effect (Stewart and Rogoff, 1919–1921). Crowden, 1929, showed that the adrenal glands can be partly depleted by subjecting the animal to *external cold. Anesthesia* by chloroform, ether or urethane leads to discharge of epinephrine from the adrenal medulla (Bhatia and Burn, 1933). *Stimulation of sensory nerves* does not influence the epinephrine output (Stewart and Rogoff, 1924). Older methods gave deceptive results, partly because they did not really measure epinephrine and partly because they overlooked the important influence of the rate of blood flow through the adrenals. If the epinephrine output is constant, as is ordinarily true, then the concentration must vary with the rate of the blood flow through the adrenals. This is indeed so (Stewart and Rogoff, 1917).

Emotional States.—Imperfect methods of epinephrine estimation led to claims that emotion, fright, and such like states increase the epinephrine output (Cannon *et al.*) and diminish the epinephrine store (Elliott, 1912). Stewart and Rogoff, 1920, failed to confirm these claims by more exact methods; they found, moreover, that emotional reactions are quantitatively the same whether epinephrine reaches the blood or not.

Epinephrine Output and Blood Pressure.—The concentration in the blood never attains the level where it could affect the blood pressure except in pheochromocytomas (G. F. Cahill, 1948). Hoskins and McClure, 1912, pointed out that if epinephrine persisted normally in the circulation, it would result in inhibition of peristalsis, since the intestines are much more sensitive than the blood vessels. Trendelenburg, 1915, also found that the concentration in normal blood could not be over 1 in 1 or 2 billions, and is probably smaller—too small to affect the blood pressure or intestine. Further, Hoskins and McPeek, 1913, emphasized that the small quantity which could possibly reach the circulation would dilate instead of constricting the blood vessels. The fact that the adrenal glands do not normally contribute to the maintenance of vascular tonus is shown by temporarily *clamping the adrenal vessels.* The blood pressure does not fall while the clamp is applied (within forty hours; Austmann *et al.*, 1917), but only as death approaches; nor does it then rise when the clamp is removed (Hoskins and McClure, 1912).

Low Blood Pressure and Shock.—Stewart and Rogoff, 1914, showed definitely that the output of epinephrine and its concentration in the general circulation are not altered by low blood pressure. The concentration in the adrenal vein rises, but merely because the blood flow through the glands falls with the blood pressure, and the epinephrine is therefore less diluted. Etherization tends to lower the epinephrine store.

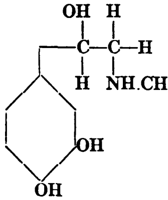
Constrictor Substance of Serum.—Normal serum has a constrictor effect on blood vessels. This was at first attributed to epinephrine (Trendelenburg); but it was shown by G. N. Stewart, 1911, and confirmed by others, that serum stimulates all smooth muscle directly and lacks the sympathomimetic inhibitory action of epinephrine, for instance on the intestines. This constrictor substance has therefore no relation to epinephrine It is formed mainly in the process of clotting (O'Connor, 1912) and increases with the age of the serum (Handovsky and Pick, 1912).

Suprarenal Testing.—Gravimetric and volumetric methods are not applicable, and recourse must be had to colorimetric and physiologic methods. For fairly large quantities, the effect on the blood pressure of mammals is commonly used. A standard procedure is described in the U.S.P. The Trendelenburg method of frog perfusion has also been widely employed. Various other methods are discussed in the papers of G. N. Stewart, 1911; Tiffeneau, 1915; J. Lévy, 1939. Folin, Cannon and Denis, 1913, described a sensitive colorimetric test, which gives good agreement with the blood pressure method. The colorimetric methods were reviewed by Barker, Eastland and Evers, 1932. Suprarenal extracts contain some *choline.* This is responsible for the depressor effects produced by such extracts after the removal of their epinephrine (Hunt, 1900).

Epinephrine, U.S.P. (Adrenalin, levo-methylamino-ethanol catechol, suprarenalin, l-suprarenin), is slightly sol. in water, alc., ether, fixed or volatile oils. *Adrenalin Tablets,* N.N.R., contain 0.33 or 1 mg. as borate. They form a 1:1000 solution when dissolved in ⅓ or 1 cc. of water. *Suprarenin,* N.N.R., is a brand of synthetic epinephrine (levorotatory).

Epinephrine Solution, U.S.P. (Epinephrine Hydrochloride Solution, Epinephrine Solution, 1:1000), is a 1:1000 watery solution of epinephrine, rendered soluble with hydrochloric acid, sometimes with small quantities of antiseptics, such as 0.1 to 0.2 per cent of sodium bisulfite. This makes them more irritant to the conjunctiva and subcutaneous tissue (Tainter, Throndson and Lehman, 1937), and doubles their toxicity with hypodermic and intramuscular injection, probably by hastening absorption, for it lacks this effect with intravenous injection (R. K. Richards, 1943). The undiluted, aseptic solutions keep fairly well. On dilution they oxidize in a few hours, acquiring a pink to brown color. This is favored by alkalis, delayed by acids. The alkaloid is a reducing agent and gives a pink or red color with oxidizing substances such as iodine (Ewins, 1910). Ferric chloride produces an emerald green color, which turns purple and carmine on adding an alkali. The U.S.P. requires the solution to be assayed by its effect on the blood pressure of atropinized dogs. The solution is intended for local use, and is not necessarily sterile. **Epinephrine Injection,** U.S.P., a sterile watery solution prepared with hydrochloric acid; usually available in containers of 1, 10 and 30 cc. of 1:1000 solution. Average dose, subcutaneous or intramuscular, 1 mg. of epinephrine. *Epinephrine Inhalation,* U.S.P. (Epinephrine Hydrochloride Spray), a 1:100 solution in water, prepared with the aid of hydrochloric acid, is used solely in asthma and hay fever, by oral insufflation of a fine mist. *Epinephrine Suspension in Vegetable Oil,* 1:500, N.N.R., is used in allergies to prolong the action of intramuscular injection, starting with 0.2 to 0.5 cc. and increasing cautiously to 1.5 cc. = 3 mg. of epinephrine. The oil may produce fibroses and scars.

Related Catechol Alkyl Amines.—Many changes may be introduced in the alkyl chain of epinephrine.



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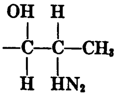
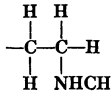


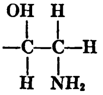
$-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{HN_2}{C}}-CH_3$

Cobefrine



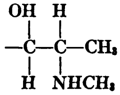
$-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{NHCH_3}{C}}-H$

Epinine



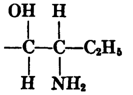
$-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{NH_2}{C}}-H$

Arterenol



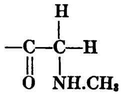
$-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{NHCH_3}{C}}-CH_3$

3,4-Dioxyephedrine



$-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{NH_2}{C}}-C_2H_5$

Ethylnorsupra-renine



$-\underset{O}{\overset{\|}{C}}-\overset{H}{\underset{NH.CH_3}{C}}-H$

Kephrine

Arterenol (demethylated epinephrine, noradrenaline; supposedly "Sympathin ME") was investigated especially by Barger and Dale, 1910, and by Stehle and Ellsworth, 1927; *ethylnorsuprarenine* by W. M. Cameron *et al.*, 1938. The latter produces a primary fall of blood pressure, from peripheral vasodilatation together with constriction of the intrahepatic veins, pooling the blood in the splanchnic area. The heart is accelerated and its output increased. Repeated injections reverse the fall to rise of pressure, with increased sympathetic response similar to that of epinephrine. *Cobefrine* has the same side actions as epinephrine and no material advantage (Tainter, 1939).

Kephrine Hydrochloride, N.N.R. (Stryphnon), differs from epinephrine in having a ketone group in place of the secondary alcohol group. It was prepared by Stolz, 1904, as the last step in the synthesis of epinephrine. Its pharmacology was studied by Otto Loewi and Meyer, 1905. Its actions closely resemble those of epinephrine, but are less potent and more persistent, and its solutions are more stable. Local effects require about ten times, and the systemic pressor action sixty times, the dosage of epinephrine (Kollert and Rezek, 1925). It is used chiefly as local hemostatic, especially in the form of impregnated gauze (Albrecht, 1923). The vasoconstriction lasts over an hour. Little is absorbed, so that there are no systemic effects. It is inactive by mouth. It has been injected hypodermically against asthma (2 cc. of 0.5 per cent) (Sumegi and Haintz, 1929). It has no special advantage over epinephrine and may produce considerable anxiety complex.

◆

E'PHEDRINE

This alkaloid was first isolated by Nagai, 1887, from Ephedra equisetina, a plant, (Ma Huang) used as medicine by the Chinese since antiquity. Most of the present supply is probably synthetic (Chen, 1927). Its chemical structure differs from that of epinephrine by the absence of the two phenolic hydroxyls. Its effects on the circulation, intestines, bronchi, iris, and so forth, are superficially similar to those of epinephrine. They require larger doses, but are more lasting, owing probably to its much greater stability and resistance to oxidation. They can be produced by oral administration. Unlike epinephrine, it is not sensitized by cocaine or by denervation. It also stimulates the central nervous system. A number of isomers with similar actions are known. Ephedrine is used therapeutically in hay fever and asthma, where it is less effective than epinephrine, but more convenient; as a mydriatic with minimal effect on intra-ocular tension; and as a stimulant to respiration, especially against barbiturate poisoning in conjunction with metrazol or picrotoxin. (Review, K. K. Chen and Schmidt, 1930, Medicine [Baltimore] *9:* 1–117, includes related substitutes.)

Species of Ephedra grow in different parts of the world. Chen and Kao state that the Chinese species contain only the official levorotatory ephedrine, while the same species and other varieties from Europe yield only dextrorotatory pseudo-ephedrine. Read and Feng, 1927, did not find ephedrine in the California species. East Indian species range from rich to none. Ephedrine exists in the seed of another, totally unrelated Indian plant, Sida cordifolia, which was also used in folk medicine. Ma Huang also contains another alkaloid, *ephedine*, which lowers blood pressure and has other complex actions (Chen, Anderson *et al.*, 1935).

The chemical structure of ephedrine, α-hydroxy-β-methylamino-propyl-benzene, differs from epinephrine chiefly by lacking the two phenolic hydroxyls. These are responsible for the susceptibility of epinephrine to oxidation, while ephedrine solutions are stable indefinitely. This may also explain why ephedrine is active by mouth. Another difference is that the side chain in epinephrine contains only one asymmetric carbon and therefore has only one pair of optical isomers, while ephedrine has two asymmetric carbons and four optical isomers. These have been synthetized (Spaeth and Goehring, 1920). The ephedrine isomers are convertible into each other, but more easily into pseudo-ephedrine. Their chemistry is reviewed by Chen and Schmidt, 1930.

The pharmacologic actions of the ephedrine isomers (reviewed by Swanson, 1932) are generally similar, but they differ somewhat, especially toward antagonists. Quantitatively, the (natural) levo-ephedrine is about twice as active as the dextro, in its peripheral actions and toxicity, so that the (synthetic) racemic (ephetonine) is about three-fourths as potent as the levo. Either may be used clinically (Pak and Read, 1928). Jarowski and Hartung, 1943, conclude that the optimal configuration for physiological activity exists in the isomers when the phenyl-bearing carbon is levo; the carbaminic, dextro.

Pseudo-ephedrine is considerably weaker for the blood pressure and pupil, about equal for the bronchial dilatation and nasal vasoconstriction, and stimulant to the myocardium, where ephedrine is depressant in large doses (Pak and King, 1930).

Synergists and Antagonists.—The resemblance between ephedrine and epinephrine suggests an identical mechanism. This appears contradicted by the observations on antagonism and with denervated organs, although the fundamental significance of the difference is not clear. *Denervation and cocaine,* which sensitize the vasoconstrictor and cardio-accelerator responses for epinephrine, do not do so for ephedrine, or for tyramine (Tainter and Chang, 1927). Indeed, cocaine materially decreases these responses for ephedrine (De Eds, 1927; Pak and Read, 1928); but Thienes, 1930, states that it increases the uterine response. *The ergotamine reversal* of the blood pressure response of epinephrine does not extend to ephedrine with ordinary doses (De Eds and Butt, 1927; Nagel, 1925); but this difference appears to be only quantitative, for ergotamine decreases the ephedrine responses, and reversal may be secured with small doses of ephedrine and large doses of ergotamine (Curtis, 1928; Swanson, 1929). *Ephedrine and epinephrine* are synergistic with considerable potentiation for the pressor response, the blood vessels and the uterus (Csépai and Doleschall, 1928), but the uterine inhibition by epinephrine is counteracted by ephedrine (De Eds, 1927). In perfused mammalian legs, Burns, 1932, found the presence of epinephrine in the perfusion fluid essential for both constrictor and dilator response to ephedrine and tyramine.

Stability in Circulation.—Ephedrine is excreted unchanged in the urine (D. Richter, 1938). Perfusion through heart-lung-liver preparations of dogs for three hours does not destroy or fix any ephedrine, in contrast to epinephrine, which would disappear entirely, and nicotine and strychnine, which would be greatly weakened (Thorp, Essex and Mann, 1933).

Bronchial Action and Asthma.—Ephedrine is employed extensively against bronchial asthma, especially as a preventive (Middleton and Chen, 1926). It is less effective than epinephrine, but can be taken by mouth (20 to 50 mg., $\frac{1}{3}$ to $\frac{5}{6}$ grains) and the effect is more enduring. The best results are obtained in allergic asthma, fair in reflex and least in infections (Leopold and Miller, 1927).

Studies of the bronchial air-way in animals by the lung plethysmograph (Swanson) and by bronchial perfusion (Warnant, 1929; Pak and King, 1930) show that epinephrine, ephedrine, pseudo-ephedrine and hordenine all dilate in high dilutions (1 per 5 millions for ephedrine perfusion), and antagonize both parasympathetic stimulants (pilocarpine, physostigmine and arecoline) and "muscular" stimulants (histamine, pituitrin, ergotamine and anaphylaxis), while atropine relieves only the parasympathetic constriction. Perfusion and relatively high concentrations (1:10,000) with ephedrine and especially pseudo-ephedrine may constrict the bronchioles, as may also epinephrine (Pak and King). Quantitative comparisons of tyramine, hordenine and related amines were made by Alles, 1933.

Allergic Reactions.—Ephedrine (by mouth or locally) is effective in a considerable proportion of patients with hay fever, urticaria and other allergic reactions, but it is not so potent as epinephrine. On the other hand, ephedrine itself occasionally produces dermatoses (ten cases reported to 1933), with eczemas and erythema, sometimes after absorption, but especially after local application, and with positive scratch test which is negative for epinephrine (Abramowitz and Noun, 1933, ref., J.A.M.A., *101:* 1191).

Blood Pressure.—Small doses (0.01 to 0.2 mg. per Kg. intravenously for dogs, Ding, 1929) raise the blood pressure for ten to fifteen minutes. Large doses (6 to 10 mg. per Kg.) and close repetition of small injections produce less rise and actually lower the pressure (Kreitmair, 1927). This is probably due to cardiac injury, for epinephrine and tyramine may still raise the pressure at this point (Chen and Meek, 1928). Clinically, oral administration of 50 to 400 mg. raises the systolic pressure an average of 30 mm. for five hours. The diastolic pressure is also raised. The hypertension, through the vasoafferent reflexes, tends to stimulate the vagus and to depress the vasoconstrictor and respiratory center, as with epinephrine (Heymans *et al.*, 1933). The pressure rise potentiates considerably with epinephrine, as also the effects on most other organs (Koppanyi and Luckhardt, 1931). The persistent pressure rise suggested trials of ephedrine against hypotension, circulatory collapse, shock and hemorrhage; but vasoconstriction can only be of temporary benefit with these conditions. Its intravenous or spinal injection is probably more valuable to counteract and especially to prevent the fall of pressure during spinal anesthesia, as has been confirmed on dogs (Burch and Harrison, 1931). Clinically, 25 to 50 mg. may be injected by vein or hypodermically (Lundy, 1933; Weinstein and Barron, 1936).

Cardiac Effects.—The clinical response is generally unimportant. The heart rate is usually quickened, sometimes slowed (Middleton and Chen, 1926), occasionally arrhythmic. The acceleration is due to peripheral stimulation of the sympathetic innervation, the slowing to aorto-carotid reflexes from the pressure rise. Ephedrine, 30 mg. two or three times daily, is sometimes effective against the Adams-Stokes heart-block syndrome (J. E. Wood, 1932). Severe cardiac disease contraindicates ephedrine, partly because of the anxiety complex which it induces. Large doses are directly depressant to the cardiac muscle; but it does not induce ventricular fibrillation after chloroform, as does epinephrine (La Barre, 1928); nor does it cause myocardial degeneration when used with sparteine as does epinephrine; it does not produce the atheromatous lesions which epinephrine causes in rabbits (di Mattei, 1931).

In dogs, with intact vagi, intravenous or hypodermic injections, to 30 mg. per Kg., usually slow the heart rate, presumably by the pressor aorto-carotid reflex. The minute output, measured by Fick's method, may be increased notwithstanding the slowing (C. P. Wilson *et al.*, 1928). With divided vagi or after atropine the rate is generally quickened; above 30 mg. per Kg. atropine does not prevent slowing, indicating direct muscular depression (Chen and Meek, 1926). The cardiac depression was studied electrographically by Meek and Seevers, 1934. They describe four stages in unanesthetized dogs. Even therapeutic doses may produce cardiac irregularities, especially in the ventricular rhythm in man and dogs. Narcotic doses of barbiturates are somewhat protective. When administered with atropine, ephedrine may increase the sinus rate to 200, often with AV block (Seevers, 1933). Digitalis in doses which have no effect on the electrocardiogram if they are injected alone, doubles the duration of the ephedrine arrhythmia and changes the type to preponderantly ventricular (Seevers and Meek, 1935). Perfused hearts are stimulated by dilute solutions (1:10,000 for turtles, 1:100,000 for rabbits) with increased rate and amplitude. Ten times stronger concentration depresses the rate, but not the amplitude. Still higher concentrations (1:100 for turtles, 1:2000–1000 for rabbits) cause partial heart block and diastolic arrest (Chen and Meek, 1926; Barlow and Sollmann, 1926; Kreitmair, 1927). The effect of ephedrine esters is similar, but generally less stimulant and more toxic (Dulière, 1927). The depression and toxicity appear to be directly muscular (Barlow and Sollmann, 1926). The stimulant phase is primarily sympathetic. Chopra *et al.*, 1931, assume also parasympathetic and muscular stimulation.

The *potency for cardiac acceleration* increases in the sequence of amphetamine < ephedrine < neosynephrine < propadrine < tryamine < arterenol < cobefrine < epinephrine (Crismon and Tainter, 1939). The cardiovascular effects of a series of aliphatic sympathomimetic amines are reported by D. F. Marsh, 1946.

The **vasoconstrictor action** is used especially in rhinitis, sinusitis and hay fever to shrink the congested mucous membrane. This may be accomplished by oral or by local administration, in contrast to epinephrine; indeed, the oral is generally preferred, even with hay fever (Leopold and Miller, 1927). For local use it is applied as sprays, or "drops" containing 0.5 to 2 per cent of an ephedrine salt or 1 per cent of the base in oil. With a 3 per cent spray, the shrinkage of congested turbinates begins within a few minutes and persists up to three hours. It is most effective if used early in the paroxysm (Fetterolf and Sponsler, 1925). The shrinking of the mucosa is felt as diminished obstruction and may be demonstrated by direct inspection or quantitatively by nasal plethysmograph (Swanson, 1931) or thermopyle (Liljestrand and Schmidt 1930). The latter found that the constriction is not followed by increased dilatation. Phenylethanolamine gave more persistent constriction.

Vascular Perfusion.—In general, low concentrations constrict and high concentrations (about 0.5 per cent) dilate, as do prolonged perfusions with dilute (0.005 per cent). The relative response varies with different organs: the spleen gives prolonged constriction; the kidney constriction is followed by dilatation; the intestine, generally dilatation. Pseudo-ephedrine acts similarly and is additive (Chen and Meek, 1926; Loo and Read, 1928). Tyramine produces but little constriction in the perfused frog's leg; this is augmented by epinephrine, but not by pituitrin (Burns, 1932). Observations of blood vessels in a chamber of the rabbit's ear show that ephedrine contracts the arteries, but not the smaller vessels (Hou, 1932).

Splenic contraction and increase of circulating erythrocytes are distinctly less than with epinephrine; indeed, the response is inconstant (Gasparini, 1928). In guinea pigs, ephedrine increases the red cells, leukocytes and platelets even after excision of the spleen. This is probably due to extrusion from the bone marrow (Simpson, Levy and Cadness, 1936).

The urine flow is increased by small doses of ephedrine (½ to 1 mg. per Kg.), probably from the accelerated blood flow caused by the high blood pressure and renal dilatation. Pseudo-ephedrine is more effective. Large doses suppress diuresis, especially in anesthetized animals and under phenobarbital (Chopra, Krishna and Ghose, 1931)

Mydriasis without cycloplegia occurs readily on local or systemic administration (in contrast to epinephrine, which acts more powerfully, however, on the denervated iris than does ephedrine). It is utilized clinically (locally, as 1 to 10 per cent, using 2 per cent of ephedrine sulfate for light iris and 4 per cent for dark, with or without the addition of 0.1 per cent of homatropine) for routine ophthalmic examination when cycloplegia is not required. The mydriasis lasts from three to five hours, with slight cycloplegia for one to two hours; the pupil reacts to light even with the 10 per cent solution. There is slight smarting and congestion of the conjunctiva, lasting half an hour; above 5 per cent it sometimes causes negligible headache and nausea. Pseudo-ephedrine is not used in ophthalmology, as the effects are weak and uncertain, even in the 10 per cent solution (H. J. Howard and Lee, 1927). Chinese and Negroes are less susceptible than Europeans to mydriasis by ephedrine, cocaine and euphthalmine (Chen, 1928).

Local Anesthetic Action.—Frog's sciatic conduction is blocked by 5 per cent ephedrine hydrochloride; intracutaneous injection of 0.1 per cent is anesthetic in man. Rabbit's cornea is not anesthetized by 10 per cent (F. H. Schultz, 1940).

Gastric Motility.—Clinical fluoroscopic studies show immediate increase, lasting eight to ten minutes, followed by inhibition with delayed gastric emptying and slowed passage through the intestines, the effect lasting three to four hours (Trachtenberg, 1931). Oral administration of 0.065 Gm. of ephedrine sulfate doubled the normal emptying time (Van Liere *et al.*, 1936). The gastric acidity is usually unchanged, the neutral chloride is increased.

Gastric inhibition by epinephrine was reported for unanesthetized dogs by J. H. Kinnaman and Plant, 1927; for cats by E. D. McCrea and MacDonald, 1928; minute doses may cause transitory contraction (I. Marcu and Savalesco, 1928).

Intestinal Motility.—In unanesthetized dogs with intestinal fistula, Kinnaman and Plant observed relaxation and suppression of peristalis after hypodermic or oral administration of ephedrine, 5 mg. per Kg. Excised intestine is generally relaxed (Kreitmair, 1927), but may be stimulated. Patients may develop some difficulty in relaxing the *anal sphincter* after taking ephedrine for some time.

The **uterus** is less sensitive to ephedrine than to epinephrine. According to Curtis, 1929, it is generally stimulated, with gradual increase in tone and amplitude, in all animals, regardless of the response to sympathetic stimulation (in contrast to epinephrine). The stimulation is abolished by ergotamine and potentiated by cocaine (Thienes, 1930). Ding, 1929, described uterine relaxation in young guinea pigs. Clinically, ephedrine does not relax the parturient uterine contraction ring, as does epinephrine (Dodek).

Urinary Bladder.—Full doses of ephedrine may produce *vesical retention* (Balyeat and Rinkel, 1932), and patients who have taken the drug for some time may have infrequent micturition. It has been employed with considerable success against *enuresis* of children (0.03 Gm. tablet at bed time, increasing by this amount every three or four nights, if necessary, sometimes to a total of 0.3 Gm., and continuing for several months; Brookfield, 1937). Kittredge and Brown, 1944, report good results from 50 mg. at bedtime for two weeks; but in many cases enuresis resumed on discontinuing the medication.

Excised ureter, in the dog and pig, is chiefly stimulated, followed by depression with large doses. Epinephrine produces similar stimulation with lower concentrations and does not depress (Roth, 1930). Ephedrine is said to *prevent erection* in some individuals.

Glandular Secretion.—The effects are confused by the vasoconstriction, but probably are unimportant. Large doses cause salivation in dogs, perhaps by nausea. The gastric, biliary, pancreatic and intestinal secretions are not increased (Chen, 1926).

Myasthenia gravis is reported to be markedly and progressively improved in almost all patients by prolonged administration of ephedrine, generally in conjunction with aminoacetic acid. Epinephrine is ineffective (Viets and Schwab, 1939). The mechanism of this action is not known. Light and Weiss, 1934, reported that oral administration of 25 mg. of ephedrine three or four times daily produces temporary cessation of *creatinuria*. The contractility of frog's *gastrocnemius* muscle is somewhat increased by 1:1000; 1:100 produces fibrillation (Kreitmair, 1927).

In **Addison's disease**, ephedrine raises the blood pressure, but does not improve the general condition (Rowntree and Brown, 1926).

Respiratory metabolism of unanesthetized trained dogs is decreased by ephedrine (12 to 18 per cent after 100 to 850 γ), in contrast to epinephrine (J. de Moreloose, 1942).

Considerable hyperglycemia is produced, more in dogs than in rabbits. In contrast to epinephrine hyperglycemia, it is checked by barbiturates, and is presumably central (D. Campbell and Morgan, 1933). The *fat and lactic acid* of the blood are generally increased. *Tyramine* causes little or no hyperglycemia (Himwich *et al.*, 1930).

Central Actions.—Ephedrine produces phenomena of *nervous excitement*, often manifested with clinical doses as insomnia and tremors and an *anxiety complex*, especially in neurotic individuals and in women. Large doses stimulate the *respiratory center*, and in animals produce *convulsions*, which occur after decerebration, as with cocaine. This stimulation has been utilized in the treatment of *narcotic poisoning* by barbiturates (Barlow and associates, 1936), morphine (C. F. Schmidt and Livingstone, 1928), and scopolamine (Kreitmair, 1927). It also gave marked or complete symptomatic relief in a series of patients with *narcolepsy* and catalepsy (25 to 50 mg. in capsules, two or three times daily) (Doyle and Daniels, 1932; Daniels, 1934; but *amphetamine* appears to be more effective. Ephedrine increases the discharge of impulses from the central nervous system to the *sympathetic ganglia*, but blocks them within the ganglia, so that they are not effective. The central sympathetic stimulation is independent of the respiratory stimulation (Marrazzi, 1939).

Intracisternal injection causes especially strong stimulation of the respiratory center and is effective against respiratory paralysis by procaine (Isenberger and Rice, 1936).

Temperature.—Injection of 10 mg. of ephedrine causes a rise of 1.5° C. in rabbits (Ding). *Ephetonine* (synthetic racemic ephedrine) produces sweating with fall of temperature by 1° to 2° C. (Seeber, 1933).

Local anesthesia results from direct application of 5 per cent ephedrine hydrochloride to frog's sciatic nerve, or 0.1 per cent intracutaneous injection in man. The cornea is not anesthetized by 10 per cent solution (F. H. Schultz, 1940).

Toxic Effects.—The anxiety complex may be annoying, but no serious effects have been reported from single doses as high as 400 mg. (6⅔ grains), or from 150 mg. every three hours day and night. Prolonged use does not seem to produce cumulative effects (Chen and Schmidt, 1930); indeed, it may induce some tolerance (Althausen and Schumacher, 1927). The fear has been expressed that the psychic excitation of ephedrine would lead to addiction; and large doses administered to animals over long periods have produced delirious and maniacal phenomena resembling those of cocaine, especially in animals habituated to this alkaloid (Seevers, 1930). These have not been reported in the extensive clinical use of ephedrine.

***Ephedrine Hydrochloride,** U.S.P., is obtained from several species of Ephedra or synthetically. It is freely sol. in water (1:3) or alc. Dose, 15 to 60 mg., ¼ to 1 grain; for nasal instillation, 0.5 to 2 per cent; for ophthalmic, 4 per cent. A 1 per cent solution is reported to produce a stinging sensation in the nose, which is absent with the *sulfate*, also official. *Ephedrine Sulfate Tablets*, U.S.P., are usually available as 15, 25, 30 and 45 mg. (¼, ⅜, ½ and ¾ grains). *Capsules* usually contain 30 or 50 mg. *Ephedrine*, U.S.P., the free base, is sol. in water, alc., and liquid petrolatum. *Racéphedrine hydrochloride*, N.N.R., also available as sulfate, contains the racemic (d-1) synthetic alkaloid. It is about half as potent as the official levo-ephedrine, but is used in the same dosage.

Cinnamyl ephedrine is reported by F. H. Schultz, 1940, to produce direct depression of smooth muscle, antagonistic to barium and mecholyl, and lowering blood pressure. It produces *local anesthesia*. It is about ten times more potent than cocaine on rabbit's cornea (but 1 per cent produces irritation); twenty times more potent than procaine on human intradermal injection; slightly more potent than procaine for spinal anesthesia. Frog sciatic is blocked by one per cent. The *d* and *l* are about equally potent, but the *l* is about half as toxic as the *d* (F. H. Schultz and Barbour, 1942).

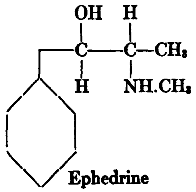
Other phenyl alkylamines are derived by altering the side chains in ephedrine. The following are the more important:

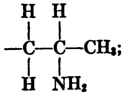
AMPHET'AMINE (BEN'ZEDRINE)

This synthetic base (alphamethylphenethylamine, betaphenylisopropylamine, racemic desoxy-nor-ephedrine) differs from ephedrine in a somewhat simpler side chain. It is used to produce similar local vasoconstriction in rhinitis and the like, with the convenience that it may be administered by inhalation. Its systemic administration (as the sulfate) relaxes spastic contraction of the digestive tract. It stimulates psychic activity more than does ephedrine, and is employed against narcolepsy and depressive neuroses, but should not be used promiscuously. It has been tried clinically against the respiratory depression of morphine and appears to be more effective than ephedrine, metrazol, caffeine or nikethamine (Handley and Ensberg, 1945). Overdosage causes restlessness and insomnia, and exceptionally serious immediate reactions. It may produce mild addiction. The rise of blood pressure contraindicates its administration in hypertension and in coronary disease. Its pharmacology is described by Detrick *et al.*, 1937. It is partly sympathomimetic, partly musculotropic. In man, after oral administration of 20 mg. of amphetamine sulfate, about 9 per cent is *excreted* by urine in twenty-four hours, 50 per cent in forty-eight hours. The remainder is slowly inactivated in the body; less if the organs have been injured by carbon tetrachloride (K. H. Beyer and Skinner, 1939).

The *vasoconstriction of the upper respiratory mucosae* is comparable to ephedrine, and is less intensive, but more lasting, than with epinephrine. It is useful especially in sinusitis and rhinitis; it is less effective than epinephrine against the allergy of hay fever, and it is probably unsuccessful against spasmodic asthma, as it contracts the *bronchiolar muscle* (Sollmann and Gilbert, 1937).

There is no apparent relation between the pressor and bronchiolar potency of the phenylpropylamine derivatives (B. E. Graham and Cartland, 1944).


Ephedrine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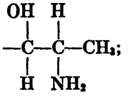
Amphetamine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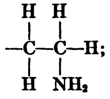
Própadrine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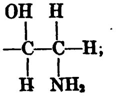
Phenylethylamine


$-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{NH_2}{C}}-H;$

Phenylethanolamine

Amphetamine (base) is marketed for this purpose as *Benzedrine Solution*, 1 per cent in liquid petrolatum, aromatized with lavender oil; and as an *inhaler*, charged with 0.325 Gm., with menthol and lavender oil. Only one or two inhalations should be taken at intervals of an hour, to guard against *overdosage*, which causes marked mydriasis, insomnia, inability to relax, dryness of the mouth and sometimes persistent rise of blood pressure. *Skin eruptions* occur rarely (J. S. Ersner, 1943). *Gross overdosage* produces extreme restlessness, rapid pulse or heartblock, pallor, rapid shallow respiration, collapse, sometimes ending fatally after several hours of coma (A. J. Hertzog *et al.*, 1943; H. A. Rosenbaum, 1943; S. P. Waud, 1938, gives a detailed description).

Control of Obesity.—Continued administration of amphetamine or propadrine results in loss of body weight, in rats as well as in man, owing to depression of appetite, which makes it easier to enforce dietary restriction. S. C. Freed, 1947, attributes this to a feeling of well being, doing away with the nervous tension that leads to overeating. Hawirko and Sprague, 1946, recommend d-amphetamine, 2.5 to 5 mg. with each meal, as producing less excitement and insomnia than the usual dosage of amphetamine, 5 mg. of the sulfate at 8 A.M. and 10 A.M. Clinical digestive disturbances include nausea, eructations, flatulence, abdominal cramps, disturbed bowel regularity (Ersner, 1940). A temporary increase of about 15 per cent in *oxygen metabolism* follows oral administration of 20 mg. of amphetamine (G. A. Emerson and Abreu, 1944). *Rats* show no material increase of energy metabolism, and no material effect on digestion. Food intake is impaired for about a week, when appetite returns even if the drug is continued. Propadrine proved less effective than amphetamine, but also less excitant (M. L. Tainter, 1944).

Irradiation Sickness.—Amphetamine and dextro-desoxyephedrine are credited with improvement, presumably by counteracting increased capillary permeability (E. L. Jenkinson and Brown, 1944).

Acute effects on the circulation, as observed in dogs, consist in prolonged rise of blood pressure, marked slowing of the heart (chiefly reflex) and increase of cardiac amplitude. The *urine flow* is increased. The *spleen* contracts briefly, with prompt *erythrocytosis*. The *respiration* is moderately increased from the carotid sinus reflex. Toxic doses injure the myocardium (Dautrebande, Philippot and Charlier, 1939). The vasoconstriction is not enhanced by cocaine or completely reversed by ergotamine (E. M. Boyd and Connell, 1937). Repetition of moderate doses produces fall of blood pressure instead of rise (Alles, 1933; Tainter, 1933). The mechanism of this depressor response is not clear. It is not prevented by division of the vagi, atropine or carotid sinus denervation, but is enhanced by cocaine (Pinkston *et al.*, 1939).

The *frog heart* responds with increased rheobase and chronaxie. The *sciatic nerve* shows increased rheobase and maintained chronaxie. The *gastrocnemius muscle* gives increased rheobase and decreased chronaxie (B. Günther, 1942).

Amphetamine sulfate against gastro-intestinal spasm was introduced by Myerson and Ritvo, 1936, for roentgenologic examinations and to distinguish between spastic and organic lesions. Oral administration of 20 to 40 mg. promptly relaxes pyloric and colonic spasm, the effect starting in five minutes, reaching its maximum in half an hour, and disappearing in an hour. The tonus of the stomach is moderately decreased; its peristaltic action is much less affected and sometimes increased. The emptying time of the spastic stomach is somewhat shortened. In normal men and dogs the beginning of gastric evacuation is hastened to about 40 per cent, probably by increased tonus of the stomach before the pyloric tonus increases. The time of complete evacuation is lengthened by about 20 per cent by inhibition of gastric tonus and possibly increased pyloric tonus (K. H. Beyer and Meek, 1939; Van Liere and Sleeth, 1938). In *seasickness*, J. Hill, 1937, reported prompt improvement in a third of the patients after 10 to 20 mg. of benzedrine sulfate, but systematic trials show that it has no value either for prevention or treatment (Holling *et al.*, 1944).

Amphetamine has relatively little effect on the *small intestines in situ* (Beyer and Meek, 1939). *Excised intestines* are relaxed by small doses; with higher concentrations this is followed by stimulation. Ergotamine, atropine and nicotine decrease the inhibition, but have less effect on the stimulation. Cocaine does not sensitize to either action (Detrick *et al.*, 1937; E. M. Boyd, 1938). Excised intestines of dogs respond with relaxation of tonus and decreased excursions; the colon is much more sensitive than the small intestines (Farah and Pinkston, 1940). Myerson and Ritvo, 1936, reported therapeutic benefits from benzedrine against spastic colitis, but the response is variable and clinically unsatisfactory (D. H. Rosenberg, Arens *et al.*, 1938), and the side effects may be disturbing. It may produce spasm of the *rectal and urinary sphincters* (D. M. O'Connor, 1937). The *gallbladder* is relaxed or not affected (J. Flexner, Bruger and Wright, 1938). The *uterus* of virgin guinea pigs responds with prolonged spastic contraction, similar to ephedrine (E. M. Boyd, 1938).

If a 0.5 to 2 per cent solution is applied to the abdomen of fireflies, their intermittent glow becomes continuous and persists for hours; similarly with the golden glow of the morning-glory beetle. Amphetamine has no effect on the luminescence of ctenophore jellyfish (J. Seifter, 1945).

The minimal lethal dose of amphetamine sulfate ranges from 5 to 150 mg. per Kg. in various kinds of animals. Continued administration at first increases susceptibility to large doses, then induces some tolerance (W. E. Ehrich *et al.*, 1939). Those which survive repeated large doses suffer no apparent injury (W. E. Ehrich and Krumbhaar, 1937). The hypodermic MLD for rats is 25 to 35 mg. per Kg. (Alles, 1933).

Mental Activity.—With normal individuals 10 to 30 mg. of amphetamine sulfate by mouth (and proportionate doses for children, Bradley, 1937) tends to increase mental alertness and motor activity to the point of restlessness, and to facilitate the flow of thought, generally at the expense of concentration, to increase loquacity, induce a rather fictitious sense of fitness, and to diminish fatigue, sleepiness and malaise. These stimulant effects occur in one-half to three hours (much faster with inhalation) and last three to nine hours (Peoples and Guttmann, 1936; Myerson *et al.*, 1936; Davidoff and Reifenstein, 1937). They led to the use of benzedrine as a spur ("pick-me-up" or "pep" pills) against fatigue and sleepiness in periods of stress, but they obscure the natural danger signals of fatigue, and the stimulation may be followed by insomnia, increased fatigue, nervousness, irritability and melancholia.

"Doping," by a single dose of 10 mg. of amphetamine sulfate for a "spurt" of temporary stimulation, may be justified to meet emergencies, in severe and extreme fatigue. It may be repeated in six to eight hours, but not more than three doses should be taken. It should not be used if the emergency continues more than twenty-four hours. If the situation requires good judgment, the dose should be only 5 mg.

Methyl amphetamine is said to be somewhat more effective for "doping." It is used for this purpose in Germany as "*pervitin*," in Argentina as "*estimulex*" (P. O. Wolff, 1943).

Fatigue of voluntary work is inhibited by 10 to 40 mg. of amphetamine more effectively than by ten times as much caffeine (Alles and Feigen, 1942). The effect of 10 to 20 mg. on work output (bicycle ergometer) varies considerably in different subjects, but may attain 60 per cent. The dextro is more effective than the levo-isomer (P. K. Knoefel, 1943). The ability for a spurt of physical performance by fatigued soldiers is definitely improved. If the individual is sleepy, but not otherwise, performance in reading and simple arithmetic is also improved, but not with complicated problems (N. Alwall, 1943).

Doses of amphetamine larger than 20 mg. do not appear to add materially to the exhilaration, but rather to its duration; but large doses develop high blood pressure, tachycardia and relaxation of gastro-intestinal tonus. Up to 80 mg. have been given at a single dose, and 200 mg. in the course of a day (Davidoff and Reifenstein, 1937), without serious ill effects; but one patient who supposedly took 140 mg. developed convulsions, coma for thirty-six hours, hematuria, encephalopathy and pneumonia, yet recovered (Apfelberg, 1938).

Addiction.—Individuals who feel the initial stimulation as elation or euphoria may be tempted to repetitions of the experience, which terminates rather infrequently in addiction, chronic restlessness and hyperexcitability, alternating with melancholia. As there is no tolerance and no violent craving, the drug is easily withdrawn.

Amphetamine on the Activity of Albino Rats.—For the four hours following the injection (of 3 mg. per Kg.), the activity in the revolving cages was increased to seven times that of the controls, but it was followed by decrease in the next twenty-four hours, so that the total activity was the same as that of the controls. No tolerance developed (L. V. Searle and Brown, 1938. The effects have also been studied by Ehrich and Krumbhaar, 1937). Amphetamine *retards learning*, as tested by a maze (W. L. Minkowsky, 1939). In dogs, 1 mg. per Kg. by mouth results in moderate decrease of differentiation in conditioned reflexes (Alpern *et al.*, 1943). Amphetamine and its derivatives neutralize the depressant effect of tyramine and other amines on the *respiration of brain tissue* (sliced or minced) in dextrose solution (P. J. G. Mann and Quastel, 1940).

The relative central stimulation by various sympathomimetic amines has been compared by increase of motor activity in rats (Schulte *et al.*, 1941). The phenylisopropylamines are the more active, amphetamine heading the list. Ephedrine is less potent. Epinephrine produces considerable but brie stimulation. No stimulation was observed with cobefrine, kephrine, neosynephrine, propadrine, synephrine, and tyramine.

Psychiatric Conditions.—Amphetamine sulfate relieves narcolepsy without apparent ill effects, so that the patients may lead a practically normal existence. The dosage should start with 2.5 to 10 mg. (¼ to 1 tablet) before breakfast, and be repeated at intervals as needed up to four times a day; but not in the evening, to avoid interference with normal sleep. If 20 mg. per day are not effective, larger doses are also generally ineffective (M. H. Nathanson, 1937). It is useful as a symptomatic treatment of mild depressive states and somewhat against severe psychopathic depressions. It is helpful in postencephalitic *Parkinson's disease*, especially against the oculogyric crises, the lack of energy, the day drowsiness and the night insomnia; in half to two-thirds of the patients it decreases the muscular rigidity and the tremor. These last are remedied most effectively by using it with atropine or scopolamine (atropine sulfate, 2.5 to 4 mg. three times daily; amphetamine sulfate, 10 to 20 mg. before breakfast and again at noon) (P. L. Davis and Stewart, 1938). Its value in other psychoses and neuroses is questionable. The drowsiness and hebetude of phenobarbital treatment of epilepsy may be prevented by amphetamine sulfate, 5 to 20 mg. by mouth, without increasing the number or severity of the seizures (B. Cohen and Myerson, 1938; L. J. Robinson, 1941). However, it lowers the threshold of electro-convulsions (K. C. Bailey, 1943).

Alcoholic psychoses generally respond favorably; 20 or 30 mg. a day accelerate the improvement, especially in recent cases. The acute hang-over depression may disappear in an hour or so after a morning dosage of 5 to 10 mg. (Wilbur, MacLean and Allen, 1937; Reifenstein and Davidoff, 1937). Reifenstein, 1940, confirmed that it has an analeptic effect on moderate alcholic narcosis, but that it increases the toxicity of near-fatal doses. W. Bloomberg, 1939, reports good results in chronic alcoholism from the long-continued use of amphetamine sulfate, 20 to 30 mg. daily; the euphoria apparently diminishes the urge for alcohol. Reifenstein and Davidoff, 1940, obtained rather variable results. M. Rosenbaum and Lams, 1942, reported poor results. It has also been used against *barbiturate poisoning*. It appears clinically useful in barbiturate coma, injected by vein, 10 to 40 mg. followed every half hour by 10 to 20 mg., as 1 per cent solution. Even 400 mg. appeared harmless (Freireich and Landsberg, 1946). The *relative analeptic potency of* sympathomimetic amines was investigated by Tainter, Whitsell and Dille, 1939. Prinzmetal and Alles, 1939, found the dextro isomer more effective clinically than the levo or racemic (benzedrine). Amphetamine abolishes *bulbocapnine* catalepsy (E. Spiegel, 1938).

In *chronic neuroses associated with depression, fatigue or anhedonia*, amphetamine (2.5 to 20 mg. at breakfast, sometimes repeated at noon) is generally of temporary benefit, sometimes striking, but it often fails on continued use (Myerson, 1936; Wilbur *et al.*, 1937; Reifenstein and Davidoff, 1937). It may correct the *obesity* resulting from anhedonia, but should not be used against other obesities (Myerson and Lesses, 1938). In *dementia praecox* it appears to have no effect on the catatonic or hebephrenic states (Myerson, 1936).

Analgetic Action.—Testing this by electric stimulation of amalgam-filled teeth, Goetzl *et al.*, 1943, and Burrill *et al.*, 1944, found amphetamine quite potent, alone or with morphine. Handley and Abreu, 1942, however, reported amphetamine antagonistic to the analgetic as well as to the sedative action of morphine.

Contraindications to amphetamine are hypertension, coronary disease and manic excitement.

Blood Pressure Changes on Oral Administration.—Clinical doses of 30 to 40 mg. cause considerable rise of blood pressure and also a slight rise in the pressure of the cerebrospinal fluid. The pressor effect is markedly enhanced by atropine and antagonized temporarily by mecholyl. The red and white blood cell count rises, probably mechanically. Beyer, 1939, reported that 30 mg. by mouth increase the basal metabolic rate, averaging 15.4 per cent in two and one-half hours; and continued use often leads to considerable loss of body weight (seven to twenty pounds), owing to the increased activity and decreased appetite (Nathanson, 1937). Penrod, 1941, found the basal metabolic rate slightly raised.

Preparations.—*Amphetamine Sulfate, N.N.R., the sulfate of alphamethyl-phenethylamine sulfate; racemic desoxynor-ephedrine, *benzedrine*: a white, odorless, somewhat bitter powder, freely soluble in water, slightly in alcohol. Initial dose, 2.5 to 10 mg., increasing gradually if necessary, usually not to exceed 10 to 20 mg. per day. Marketed as *tablets* of 5 and 10 mg. *Benzedrine Inhalers* contain 0.25 Gm. of the free base (a volatile liquid), together with menthol and oil of lavender.

Propadrine Hydrochloride, N.N.R., a salt of phenylaminopropanol, whose structure resembles that of ephedrine, with the methyl on the amino group replaced by H. Its actions resemble those of ephedrine closely, being probably somewhat more prolonged, with less erethismus and anxiety complex. It is used locally for vasoconstriction of mucous membranes, as 1 per cent aqueous solution or ⅔ per cent jelly; and orally in asthma, 25 mg. (⅜ grain) every two to four hours. It is claimed that it does not cause urinary retention in prostatic patients. No toxic effects have been reported.

Betaphenylethylamine differs from amphetamine only by a methyl group. It is very stable, but the blood pressure rise is brief, and on oral administration it tends to lower the blood pressure. Small doses stimulate the cardiac muscle, large doses depress. All doses contract the coronary vessels; this is followed by relaxation with large doses (Barbour and Frankel, 1915). It is not mydriatic (Chen, 1928). When phenylethylamine or tyramine is fed to rats, or injected, it increases catabolism and lowers the glycogen content of the liver (Abelin and Jaffe, 1920). Barbour, 1916, made a comparative study of the sympathomimetic and other actions of a series of *phenylethylamine derivatives.* W. S. Hambourger and Jamieson, 1936, investigated the pressor effects of a number of related alkyl derivatives.

Betaparaoxyphenyl isopropylmethylamine (*Veritol*) is reported to increase the plasma volume and to raise the blood pressure without increasing the heart rate. It has therefore been recommended to counteract shock (Zachowski and Ehnimb, 1939).

Phenylethanolamine, 2 aniline-ethanol, is closely related to amphetamine and ephedrine in chemical structure and actions (M. L. Tainter, 1929; Liljestrandt and Schmidt). It produces methemoglobin clinically and in animals (A. D. Bass *et al.*, 1943). The pharmacology of a series of *phenylisopropylamines* was investigated by Alles, 1933; and *phenylpropylamines* by Hartung and Munch, 1931.

Indolethylamine stimulates plain muscles, especially of the uterus, arteries and iris. It also has stimulant central effects (Laidlaw, 1911). Perfusion through excised liver converts it into indolacetic acid. Dogs excrete 30 per cent as indolaceturic acid (Ewins and Laidlaw, 1913). The actions of the beta isomer ("*rutamine*") were reported by Ryô, 1927.

Ptomaine Bases.—Amine bases are formed in the putrefaction of proteins, and many of these ptomaines have been isolated in crystalline form (Barger and Walpole, 1909; Hanzlik, 1916); but the phenomena of so-called "ptomaine poisoning" are due chiefly to bacterial toxins (Ecker and Rademaekers, 1926).

◆

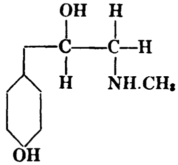
PHENYLEPHRINE

This is the levo form of a phenylethylamine derivative intermediate between epinephrine and ephedrine, containing one OH group in the meta position. Its actions come closer to those of ephedrine. It is fairly stable, and its effects are fairly lasting. It raises the systemic blood pressure on oral administration, but causes less nervousness than ephedrine (Tainter and Stockton, 1933). It does not relax the bronchi, except with concentrations a thousand times greater than with epinephrine, and not feasible in life (McIntyre, 1936).

Phenylephrine hydrochloride, N.N.R. (Neo-synephrine), is used locally as ¼ to ½ per cent solution against nasal congestion and as addition to local anesthetics (3 to 5 drops of 1 per cent to 10 cc. of the anesthetic solution). The 1 per cent solution is mydriatic. It may be sterilized by boiling.

Synephrine is the tartrate of a racemic isomer with the OH in the ortho position. It is less potent than neo-synephrine.

Other phenyl alkyl amines representing changes in the side chain of neo-synephrine, but with the OH in *para* position,



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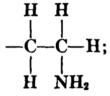
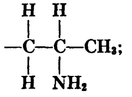


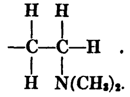
$-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{NH_2}{C}}-H$;

Tyramine



$-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{NH_2}{C}}-CH_3$;

Paredrine



$-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{N(CH_3)_2}{C}}-H$.

Hordenine

Tyramine is parahydroxyphenol ethylamine. Its actions approach closer to those of ephedrine than to those of epinephrine. The pressor effect is less potent than with epinephrine, but more lasting (Dale and Dixon, 1909)

Occurrence.—Tyramine exists commonly in the products of putrefaction, autolysis and fermentation; it is therefore present in the alimentary tract. It was isolated from ergot (which contains 0.01 to 0.1 per cent) and was prepared synthetically from hordenine (its dimethyl derivative) by Barger, 1909. Further syntheses were made by Barger and Wampole, 1910. It occurs also in the common American and European mistletoes (*Phoradendron flavescens and Viscum album*). It has not been demonstrated in other species of Phoradendron (Crawford, 1914; Ostenberg, 1915). It constitutes the "salivary" poison of certain cephalopods (Henge, 1913).

It was also called *uteramine* from its (rather feeble) oxytocic action, and *ergotamine* from its occurrence in ergot. This has led to unfortunate confusion with the ergot alkaloid of that name.

Circulation.—Intravenous injection of tyramine produces considerable rise in blood pressure, lasting two or three minutes. The heart is slowed reflexly. The rise appears to be purely vascular, judging by the diminished volume of the kidneys and intestines, and by the decreased vein flow (Bickel and Pavlov, 1912). The constrictor action is generally considered peripheral since it occurs also on excised arteries, even on the coronaries (Barbour, 1913). However, Baehr and Pick, 1916, claimed that the pressure rise of tyramine and related bases does not occur after nicotine, and Burns, 1930, found that perfusion of tyramine constricts vessels only in the presence of epinephrine. Zipf and Gebauer, 1938, concluded that the peripheral actions involve both the sympathetic endings and the muscle directly. The myocardial contractions are rendered stronger, as with epinephrine, but the effect is shorter (Kruda and Zadina, 1938).

In man, intravenous or hypodermic injection (but not oral or rectal administration) of 20 to 80 mg. of tyramine causes marked rise of systolic blood pressure and vein pressure, slowing of the heart and increase of the T wave of electrocardiograms. The cardiac output is increased, and the volume of circulating blood is considerably augmented by emptying the vein depots. *Polycythemia* and *lymphocytosis* occur as with epinephrine. Hypodermic injections should be made in the loose tissue below the clavicle, as the local vasoconstriction may prevent absorption from other locations. The effects begin in ten to twelve minutes and last five to thirty-five minutes. They are brief with intravenous injection (F. Meyer and Eckers, 1938; Downs and Eddy, 1930). The *cerebrospinal fluid pressure* varies with the circulation (Dixon and Halliburton, 1914). Injections of 5 to 20 mg. ($\frac{1}{12}$ to $\frac{1}{3}$ grain) have been tried *in collapse* without much success. Even with 60 mg., Hewlett, 1918, obtained only a transient response in infective diseases. After operations, there was generally permanent improvement; but it is difficult to exclude spontaneous recovery. Tyramine is fairly effective in arresting superficial *capillary hemorrhage,* both by local and systemic application; but its efficiency is far below that of epinephrine (Hanzlik, 1918).

Vascular Lesions.—The injection of tyramine into mice may produce temporary stasis of the capillary circulation, similar to that of inflammation (J. Wolf, 1923); but tyramine does not blue the comb of the rooster acutely (Crawford, 1913), or produce gangrene on repeated injection (Bickel and Pavlov). Daily injections of 50 to 100 mg. for three or four months into rabbits cause necrotic arteriolar lesions, similar to those of renal ischemia in dogs, and of human malignant hypertension (Duff *et al.*, 1939). Long-continued administration to dogs results in nephrosclerosis (Paunz, 1933).

Uterus.—The usual effects, as observed through the celluloid abdominal window, consist in stimulation of peristalsis and tonic spasm, analogous to that of ergotoxine (Ludwig and Lenz, 1923). The reactions show the same species differences as for epinephrine (Dale and Dixon, 1910; Acton and Chopra, 1925; human uterus, Lieb, 1915). Tyramine has been tried *clinically* as a substitute for ergot in labor, postpartum hemorrhage, operations and various gynecologic conditions. Favorable results have been reported by some (K. Abel, 1914). Others found it unreliable (Guggenheim, 1912). The doses used in these earlier experiments were probably too low. With larger doses (40 mg. plus 16 mg. of morphine, hypodermically) Barbour, 1917, recorded distinct increase of the strength and rate of labor pains, without undesirable side effect. On the contrary, tyramine counteracts the respiratory depression of morphine, so that the respiration is slightly quickened by the combined dosage. The actions of morphine on other functions are not antagonized (Barbour and Maurer, 1920).

Respiratory effects were studied by Bry, 1914.

Bronchioles are contracted by tyramine (Baehr and Pick, 1913; Golla and Symes, 1913). Accordingly, tyramine does not relieve asthmatic attacks (Hewlett and Kay, 1918).

Excised stomach is constricted (frogs).

Excised intestines are stimulated in rabbits; relaxed in dogs; first stimulated and then relaxed in cats (Manysek, 1914).

Spleen is contracted.

Gastric secretion is sometimes stimulated in cats, but not in other animals (Keeton *et al.*, 1920).

Pancreatic juice secretion after pilocarpine or secretin is inhibited by large doses of tyramine (Kageyama, 1916).

Hyperglycemia.—Continuous slow intravenous injection of 0.05 per cent of tyramine into rabbits may raise the blood sugar to 0.1–0.17 per cent, and the urine sugar to 2 per cent (Kageyama, 1916).

Anemia.—Long-continued hypodermic injections into guinea pigs (2 to 8 mg. daily for one to two weeks) produce severe anemia with the characteristics and course of pernicious anemia (Iwao, 1914). A similar result with hemosiderosis of the spleen, mesenteric lymph glands, cecum and bone marrow is produced in rabbits by intravenous injection of 0.1 Gm. of tyramine (Iwao, 1916).

Growth.—McCarrison, 1924, found that long-continued administration of tyramine to young animals retarded growth, and this was associated with diminished weight of the thymus and thyroid and increased weight of the adrenals. The effects did not disappear when the tyramine was discontinued. Adult animals were but little affected.

Fate.—*Tyramine* is in part converted into parahydroxyphenylacetic acid in the body and by surviving liver and uterus. It is completely destroyed by the isolated heart (Ewins and Laidlaw, 1910). The de-aminization of tyrosine in the animal organism was studied by Kotake *et al.*, 1922.

l-Dihydroxyphenylalanine ("*dopa*"), formed in the partial oxidation of tyrosin by tyrosinase, is structurally similar to epinephrine. The melanoblasts of the skin contain a "dopa oxidase" (B. Bloch, 1917), which converts the "dopa" to "dopamelanin"; but it is questionable whether this has any relation to natural melanin. The latter is bleached by reducing and darkened by oxidizing agents, and forms a natural oxidation-reduction system, comparable to glutathione, riboflavin and ascorbic acid, with relatively high potential (F. H. J. Figge, 1940). Intravenous or peritoneal injection of l-dopa (not of the dextro isomer) into rats produces marked and sustained rise of blood pressure, which is abolished by adrenalectomy (E. W. Page and Reed, 1945).

Hordenine, isolated originally from germinated barley by Leger, 1906, is tyramine with NH_2 replaced by $N(CH_3)_2$. As a tertiary amine it establishes a relation to choline. Its actions were studied especially by Camus, 1906. Small doses stimulate the vagus. Larger doses paralyze the vagus center, quickening the heart and raising the blood pressure. The bronchioles are dilated by stimulation of the sympathetic endings, sufficiently powerful to antagonize most constrictor drugs (D. E. Jackson, 1914). Fatal doses paralyze respiration. The substance is not very toxic. It has been used (0.5 Gm. per day) in heart disease and digestive derangements (Sarbazes and Guerine, 1909). It arrests diarrhea in dogs (30 to 40 mg. per Kg., hypodermically; Charmoy, 1912).

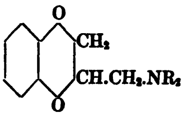
Vanillyl-ethylamine, which is methoxy tyramine, and its derivatives produce varying degrees of stimulation and depression of smooth muscle and of blood pressure. The benzl derivative is depressant without stimulation (W. E. Hambourger, 1932).

Naphazoline (Privine) Hydrochloride—2-naphthyl-(1')-methyl imidazoline hydrochloride, is a potent local vasoconstrictor, used especially in the nose and throat, applying several drops of 0.1 per cent aqueous solution for adults, 0.05 per cent for children. It sometimes produces drowsiness in children (J. I. Waring, 1945). Frequent use as nose drops commonly results in "rebound" congestion of the mucosa, although renewed application continues to produce brief constriction. The rebound is much less common with other vasoconstrictors (S. M. Feinberg, 1945). Dependence has been reported (L. E. Putnam and Herwick, 1946). Naphazoline is not consistently sympathomimetic, and appears to have some cholinergic actions. It raises the blood pressure of cats, less potently than epinephrine; retracts the nictitating membranes; salivates (not inhibited by atropine); and dilates the pupils (Yonkman, Rennick and Schwerma, 1945). The blood pressure rise is decreased but not reversed by yohimbine; it is not potentiated by cocaine. Oral or rectal administration does not significantly change the blood pressure or respiration (Craver *et al.*, 1944).

Mistletoe.—Injection of extracts of European mistletoe, *Viscum album,* produces fall of blood pressure (Gaultier and Grelant) by vasodilatation which has been attributed to excitation of the afferent depressant nerves of the heart. The heart is first slowed by increased vagal tone and then becomes rapid and arrhythmic by heterotopic stimuli (Jarisch and Henze, 1938). H. Richter and Schröcksnadel, 1938, attributed the bradycardia to reflexes from cardiac receptors, stimulating the vagus and inhibiting the accelerator centers. These actions are not characteristic of tyramine, which the plant is said to contain. Holste, 1928, suggested a saponin. Rojo, 1929, obtained a rise of blood pressure, presumably from a different extract.

Cotoin (methyl-trioxy-benzophenone) has been used against diarrhea and to check the night sweats of phthisis, in doses of 0.06 to 0.6 Gm., 1 to 10 grains. It is not antiseptic or astringent, but decreases the tone of excised intestines and uterus (Impens, 1913). In transfused frogs, it contracts the blood vessels and diminishes reflex excitability (Jodlbauer and Kurtz, 1916). It is not toxic to rabbits or to infusoria. Its excretion occurs by the urine, partly as benzoic acid (Jodlbauer and Kurtz). It is derived from Coto, the bark of an unknown Bolivian plant. This and the related "*paracoto*" barks also contain other related trioxyphenones, differing by the number of methyl groups (Jodlbauer and Kurtz, 1916).

Fourneau Sympatholytic Dioxane Derivatives.—E. Fourneau has synthesized a series of dioxanes of the general formula



which have pronounced sympatholytic actions. The most extensively studied are "F 883," diethylamino-methyl-2-dioxane (Fourneau and Bovet, 1933) and "F 933," piperidino-methyl-2-benzodioxane (Bacq and Fredericq, 1935; review, Jeanne Lévy, 1939). F 883 paralyzes the augmentor responses both to epinephrine and to sympathetic nerve stimulation; F 933 paralyzes them for epinephrine, but not for nerve stimulation; F 1081 paralyzes inhibitory sympathetic stimulation (Bovet and Demanche, 1934; Justin-Besancon, 1934).

Cardiac Effects.—F 933 depresses the excised frog heart and the denervated heart of cats, but does not greatly modify their response to epinephrine or accelerator stimulation (W. T. Hill and Myers, 1939). The resistance of the cat and rabbit heart to ventricular fibrillation by electric stimulation is raised by intravenous injection of 5 mg. per Kg. This also prevents the heterotopic rhythms of epinephrine and barium (van Dongen, 1939). The coronary vessels are constricted (L. N. Katz and Lindner, 1939).

Uterus.—In the resting cycle, 2 mg. of F 933, per Kg. have no effect, 5 mg. relax, 10 mg. contract. The relaxant effect of epinephrine is increased. During rut or after estrogen or chorionic gonadotropin treatment, small as well as large doses contract; in early pregnancy or after progestin, relaxation follows even with large doses (Duels, 1939).

Central Actions.—Both F 883 and F 933 produce psychic and motor excitement in dogs, including stimulation of the sympathetic centers; mydriasis, exophthalmos, rise of blood pressure, rapid heart; in spite of the peripheral sympatholytic action of the same doses toward epinephrine. Both substances are analgetic, intensify sleep and narcosis, and inhibit water diuresis (Zunz and Jourdan, 1935; Sivadjian, 1935).

Tuamine Sulfate, N.N.R., racemic 2-amino heptane, is a sympathomimetic amine, with a vasoconstrictor potency about twice that of ephedrine, and more prolonged. Used as 1 to 2 per cent solution on congested mucous membranes, especially in the nose. Inhalation of the vapor, from an inhaler, is also effective in acute rhinologic conditions.

◆

OXYTOCIC AGENTS

The motor functions of the uterus are autonomic, with little if any central control; but its pharmacologic reactions are chiefly toward the direct muscular agents, such as the hormone of the posterior pituitary gland, the ergot alkaloids and histamine. These oxytocic drugs (Greek, oxy = acute, tokos = birth) act essentially alike, the chief difference being in the duration of action, and thereby the facility of control. They provoke or strengthen uterine contractions. If the favorable degree is exceeded, the uterus relaxes incompletely and finally remains in spasmodic contraction. The susceptibility of the uterus to their stimulation decreases in early pregnancy (especially to pituitary), so that they are generally ineffective for emptying the uterus until near term, when its excitability suddenly increases. If the uterus is ready for parturition, moderate doses hasten delivery, but spasmodic doses may interfere with progress and cause rupture of the uterus, especially with pituitary solution. Their use at this stage is dangerous and not generally advisable. Post partum, they cause prompt contraction of the empty uterus and thereby arrest its bleeding. This is their principal field. The prompt and powerful action of pituitary extract, when 0.1 to 0.15 cc. is injected intramuscularly, is an advantage. It may be repeated if necessary; for prolonged action it may be reinforced with ergot, by mouth or rectum. Hypodermic injection of pituitary extract does not raise the blood pressure materially, but if it is important to avoid this entirely, pitocin may be used.

The following tabulation for the graphic clinical data of Barlow and Jones shows the usual time of the onset and duration of the full therapeutic postpartum action:

Agent	Channel	Ordinary Dose	Full Effect	Duration of Effect
Pituitary	intramuscular	0.1 to 0.15 cc.	7 minutes	three-fourths of an hour
Ergot, fluidextract	oral	2 to 3 cc.	10 to 15 minutes	5 hours
Ergot, fluidextract	intramuscular	2 cc.	10 to 15 minutes	4 hours
Ergotamine (Gynergen)	hypodermic	½ to 1 mg.	one-half hour	2 hours
Ergonovine	oral	¼ to ½ mg.	5 to 10 minutes	5 hours
Histamine	hypodermic	⅕ mg.	immediate	one-half hour

Ergot fluidextract is irritant and should not be used hypodermically; it may be employed by rectum. Histamine is not suitable for obstetrical use, because of its marked side actions. Tyramine is not effective clinically (Bourne and Burn, 1927).

POSTERIOR PITUITARY GLAND

The two portions of the pituitary gland, anterior and posterior, differ completely in function.

Effects Produced by Extracts of the Posterior (Infundibular) Lobe of the Pituitary (Pituitrin).—These cause powerful stimulation of smooth muscle, varying in degree, however, in different situations and under different conditions; there may even be relaxation, or a sequence of relaxation and contraction. The effects are peripheral, for they occur in denervated organs, but the peculiarities are not related to the origin of the autonomic innervation, in contrast to epinephrine (Dale, 1910); they appear more allied to those of histamine (Fuehner, 1912) or the protein "shock" poisons. The most important effects are stimulation of uterine contractions, utilized in obstetrics; persistent vasoconstriction, employed in shock; and diminished output of urine in polyurias, effectively controlling diabetes insipidus. In normal animals, the urine flow is increased for a short time after injection. The extracts are administered intramuscularly or intravenously, the latter being more effective (Pankow, 1912), but less persistent (Klotz, 1911).

Actions of minor importance include depression of the cardiac muscle (by coronary constriction); expansion of the melanophores; mydriasis; bronchial constriction; changes in intestinal peristalsis, in the flow of milk, of gastric secretion, of cerebrospinal fluid, in the coagulation of the blood and in carbohydrate metabolism.

The **active constituents** have not been isolated in pure form, but potent preparations have been obtained; for instance, that of Abel, Rouiller and Geiling, 1923, stimulates the guinea pig uterus in the dilution of 1:20,000,000,000, and is thus over a thousand times as active as the very potent histamine. The purified product may exert the characteristic oxytocic, vasopressor, diuretic and antipolyuric properties all in approximately the same ratio as the original pituitary extracts, suggesting that a single substitution is responsible for all these actions. By other and perhaps more energetic processes, fractions may be obtained in which these actions are more or less separated. Kamm and associates, 1928, and R. L. Stehle, 1933, succeeded in preparing two fractions. Those of Kamm are marketed; one, *pitocin* (oxytocin) produces almost pure oxytocic effects, about a hundred and fifty times as strong as pituitary powder, with little vasopressor, diuretic and antipolyuric effects; the other, *pitressin* (vasopressin) produces rise of blood pressure, about eighty times as actively as pituitary powder, and also the diuretic and antipolyuric, the cardiac, respiratory, intestinal and certain metabolic effects, but little uterine stimulation. Both raise the blood sugar and antagonize insulin. When mixed, in the proportions in which they represent the gland, they appear to reproduce the effects of posterior pituitary completely.

Condition in Gland.—Abel, 1930, reasoned that the fractions exist in the gland combined into a single molecule, which may be split by the reagents used by Kamm. This is confirmed by the centrifugal sedimentation rates, which indicate that pituitrin, pitocin and pitressin are cleavage products, of much smaller molecular weight than the native hormone in the glandular press juice (M. Rosenfeld, 1940).

Stability.—Alkaline, neutral and faintly acid solutions deteriorate fairly rapidly, especially on heating, but when the acidity of the extract corresponds to about ¼ per cent acetic acid, they may be boiled (but not autoclaved) without loss of activity (H. S. Adams, 1917). Excessive acidity (0.5 per cent of hydrochloric, or more than 6 per cent of acetic acid) is destructive (A. Stasiak, 1926). The oxytocic fraction is more stable than the vasopressor and antidiuretic between *p*H 2.0 and 4.5, and less stable than these beyond the extremes, in either direction. The antidiuretic is more stable than the pressor at all reactions, indicating that these are chemically distinct (H. Heller, 1939). Digestive ferments tend to destroy the activity of the extracts, although the data are somewhat contradictory (see Rees and Whitehead, 1923); possibly the decomposition is secondary to cleavage of the protecting colloid.

Origin in Hypophysis.—The structure of the posterior pituitary body is chiefly nervous, comprising nerve fibers, neuroglial cells and "pituicytes," highly branched granular cells derived from the neuroglia. It has been suggested that the active constituents are formed in the "pars intermedia" of the hypophysis, and that the pars posterior is merely a depot. Certain animals, however (whale, chick, armadillo), lack the pars intermedia, and in these the posterior (neural) part contains the pressor and diuretic principle in about the same concentration as in other animals, and also the oxytocic principle, but in somewhat smaller ratio. Both must therefore be formed in the posterior gland itself. Neither principle occurs in the anterior part. They enter the general circulation through the blood channels. Expansion of melanophores is not produced by posterior extracts from these animals, as it is with other animals, but is formed in the anterior lobe. This principle must therefore be transported into the posterior lobe from the "intermediate" portion. (Geiling, 1936; Oldham, 1938).

Fetal Glands.—The active principle appears early in fetal life (McCord, 1915).

Absence of Iodine.—Iodine is not present in any part of the pituitary gland, even after excision of the thyroid (Seaman, 1920).

Fate.—After intravenous injection of posterior pituitary extract, 25 to 30 per cent of the oxytocic and pressor principles is excreted by the urine, chiefly within the first ten minutes. The remainder is probably destroyed by the peptidases of the tissues, especially in the liver and intestinal mucosa (E. Larson, 1939).

Uterine Action.—The strongest and most important action of pituitary extract is on the uterus. Experimentally and clinically this responds by increased motor activity, increase of tonus, initiation or reinforcement of peristaltic contractions, or by firm spasm. The degree of response varies with the excitability of the uterus, and increases rapidly toward the end of pregnancy (Lieb, 1914; Knaus, 1926). Its use in obstetrics was introduced by Blair Bell, 1909. It is employed, after delivery of the placenta (0.3 to 0.5 cc. of the U.S.P. pituitary or pitocin solution), intramuscularly or subcutaneously to produce prompt and firm contraction of the uterus, and thus check postpartum hemorrhage. The action is brief, and the injection may have to be repeated; or ergot may be administered at the same time. The use of pituitary (0.1 to 0.3 cc.) earlier in labor, to initiate or strengthen labor pains and hasten delivery, is not advisable, since the powerful contraction may prevent delivery, asphyxiate the fetus, produce excessive compression, intracranial hemorrhage, premature separation of the placenta, deep laceration of the cervix, or fatal rupture of the uterus (Watson, 1923). It is also inadvisable to employ pituitary to hasten the expulsion of the placenta, since it may cause hour-glass contraction (J. W. Williams). Pituitary has been used to induce labor in the last weeks of pregnancy, but it does not produce abortion earlier, and is more effective when the os begins to dilate (Malinowski, 1919).

The degree of uterine response is greatly affected by the *sex hormones* that are preponderant in different stages of pregnancy and of menstruation. It is increased by the estrogenic hormones and inhibited by progesterone. The nonpregnant human uterus responds most actively toward the end of the menstrual cycle (twentieth day after menstruation to last premenstrual day), and least at the beginning of the cycle (third to thirteenth day) (G. K. Schultze, 1931; J. S. Henry and Browne, 1943). In early human pregnancy the uterus is irresponsive to pituitary. The response returns later in gestation, becomes very active during parturition, and is again suppressed during the involution of the uterus in the puerperium (Moir, 1934), parallel to the decline of blood estrin, becoming irresponsive after the tenth day. Some response returns if estrin is administered (W. Bickers, 1942). Analogous alterations occur in animals.

It produces marked stimulation in nonpregnant rabbits and at term. In the first half of their pregnancy it produces no effect or inhibition (Okazaki, 1927). From then to the last four days, abortion could be induced only by enormous doses, and with a delay of several days; but on the last two days of the natural term, birth resulted almost immediately from a sixtieth of the dosage required to induce a delayed labor two days previously (H. H. Knaus, 1926). *Castration* does not greatly modify the response (Athias, 1921). Heckel and Allen, 1936, confirmed that the excised uterus of rabbits which had been castrated sixteen to twenty-one days previously reacts to pituitary solution by contraction. This is more marked if they were injected with estrin; after progestin injection, the uterus fails to respond to pituitary; and if both estrin and progestin were injected, pituitary produces relaxation.

Clinical studies have been made on parturient women by introducing into the cervical canal a Vorhees bag connected with a manometer (Bourne and Burn, 1928; Moir, 1934), and by a tambour pressed on the abdomen over the fundus (Dodek). The hypodermic administration of 0.1 to 0.5 cc. produces marked peristalsis and increased tone of the uterus, perceptible in two minutes and persisting about half an hour, the tone being greater than the top of the contraction waves before the pituitary. The greater the response, the shorter the duration of labor (D. P. Murphy, 1941). The uterine stimulation may be produced by the oral administration of pituitary extract (Hamill, 1921), but the effect is too variable.

Experimental Studies.—In the body and on the excised organ, even very small doses of pituitary have a marked augmentory effect (first described by Dale, 1906), and they increase the excitability to hypogastric stimulation (Frankl-Hochwart and Froehlich, 1910). This occurs in all animals, pregnant or nonpregnant (Gunn and Gunn, 1914; abdominal window, Ludwig and Lenz, 1923). The degree of response in the nongravid uterus varies with the motor activity before the injection (S. R. M. Reynolds, 1930). *Excessive concentrations* of pituitary (also of histamine) depress the excised uterus of mice and guinea pigs; but rat's uterus is not depressed by pituitary in any concentration (Abel and Macht, 1919).

Electrolytes.—Increase of potassium or of calcium ions increases the response of virgin guinea pig uterus to posterior pituitary solution. Decrease of potassium, as also excess and deficiency of magnesium, diminishes the response (Van Dyke and Hastings, 1927). Intramuscular injection of calcium gluconate into cats markedly increases the sensitivity of the puerperal uterus to pituitary injection (Schübel, 1937).

Interaction of Epinephrine and Pituitary.—Epinephrine normally relaxes the excised uterus of guinea pigs and of nonpregnant cats; but if the uteri are first treated with pituitary, the addition of epinephrine causes them to contract (Tate and Clark, 1921).

Other Sexual Organs.—The vaginal muscle and prostate respond like the uterus; the vas deferens (Waddell, 1917) and the fallopian tubes (Gunn) do not react to pituitary, although they are stimulated by epinephrine, pilocarpine and barium. Intravenous injection into *hens* results in premature expulsion of the egg from the uterus (W. H. Burrows and Byerly, 1942). This holds also for the fallopian tubes.

Gastro-Intestinal Movement.—The effects are complex and inconstant, but pituitary solution is used clinically against postoperative *gas distention* and *paralytic ileus* (Bill and Hick, 1909), generally as prophylactic, injecting 0.5 to 1 cc. of pitressin or 1 to 2 cc. of the U.S.P. solution intramuscularly, preceding or immediately following the operation, repeating two or three times at intervals of four to six hours if necessary, and supplementing with enemas. It is used in roentgenography to eliminate gas pockets. The response is uncertain and difficult to appraise.

In normal human subjects, injection of pituitary solution rarely increases the motor activity of the stomach, duodenum or rectum (in two of twenty-three observations, Einsel and Quigley; cessation in all observations, Ochsner *et al.*, 1930; colon sometimes contracted, sometimes relaxed, Steggerda, 1938). The gastric sojourn is prolonged and the acidity diminished (Bergman, 1928).

Unanesthetized dogs give irregular responses of the intestinal tract to hypodermic injection of the two pituitary fractions. *Intravenous injection* of either fraction generally results in defecation, but with differences for the two fractions: with *pitocin* a single defecation occurs within two or three minutes, with relaxation of the circular coat (roentgenologic observation) and without collapse; with *pitressin* the defecation starts in five to fifteen minutes and continues with vomiting and retching, the stool becoming liquid. The circular coat is contracted. Marked collapse develops with fall of blood pressure (Melville, 1936).

In unanesthetized dogs with *permanent ileum fistula,* Gruber and Robinson, 1929, observed, with either pitocin or pitressin, marked temporary decrease of tonus followed by vigorous tonus waves. Quigley and Barnes, 1930, obtained depression for gastric and colonic fistulas. The effect on *propulsion of a bolus* through a jejunal loop was irregular, but predominantly depressant, for the whole extract and for either fraction (Quigley, Highstone and Ivy, 1934). In the *colon,* roentgenographic observations showed marked increase of tonus, maximal in fifteen to twenty minutes after intravenous injection of *pitressin,* but no effect after pitocin (Steggerda and Gianturco, 1936). Injection of pitressin into dogs may be followed by *gastric and duodenal ulcers,* closely resembling the clinical ulcers. They are attributed to spasm of the small blood vessels together with contraction of the gastric muscle (A. J. Nedzel, 1938, 1943). They are more common after vagotomy, less frequent after sympathectomy (M. Berg, 1942).

The *reactions of excised intestines* are complex and variable, similar to those to histamine and peptone, generally with predominant stimulation. They differ with the level of the segment, with the species, with individual animals and with the previous diet (Degener, 1922). With commercial preparations, the effects are further complicated by the depressive action of chloretone (Roth, 1917), and acidity (Gruber, 1926). E. Larson, 1928, obtained with pitressin or whole extract, definite increase of tonus in *rabbits' excised intestine,* largest in the jejunum, less in the duodenum and ileum; with large intestine, the stimulation was preceded by slight depression. With guinea pigs, the stimulation was slight, and dogs and cats usually gave no or little response. *Pitocin* had no effect on intestines of any animals.

In *mechanically obstructed dog's intestine, in situ* and isolated, pituitary produced relaxation, while physostigmine and hypertonic sodium chloride stimulated (McIntosh and Owings, 1928).

Gallbladder.—Pituitary extract may stimulate the contractions of the gallbladder in man, but without necessarily increasing the flow of bile; indeed, this may be arrested (S G. Meyers, 1928). In rabbits it has no effect on the gallbladder contractions, but diminishes the bile flow; perhaps by spasm of the duct. The effect is abolished by chloretone and by barbiturate (Adlersberg and van Goor, 1928).

Frog's Esophagus.—The circular and longitudinal muscles are both depressed by pituitary (Waddell, 1916), not by histamine; while the turtle's esophagus is stimulated by histamine (Bercovitz, 1922).

Saliva.—Intravenous injection into dogs diminishes the flow of saliva, partly by decreased blood flow, partly by direct depression of secretion. The response to pilocarpine is diminished (Solem and Lommen, 1915).

Pancreatic secretion is decreased (Pemberton and Sweet) through vasoconstriction (Edmunds).

Gastric Hyperacidity.—Pal, 1917, claimed that this is depressed to a variable degree.

Urinary Bladder.—The vesical muscle is stimulated, with increased excitability to pelvic, but not to hypogastric, stimulation (Abelini, 1919). Injections were tried in postoperative paralysis of the bladder (Hoffstätter, 1911; Serdinkoff, 1922), but seem to have been abandoned.

Excised ureter is stimulated by dilute, relaxed by more concentrated solutions.

Circulation.—The rise of blood pressure on injection of pituitary extract was described by Oliver and Schaefer, 1895. It may be preceded by a brief fall. The rise is not so high as that obtainable with epinephrine, but it is much more sustained, lasting for ten minutes to half an hour after intravenous injection. If large doses are repeated, at short intervals, the rise becomes progressively smaller (Howell, 1898), and the depressor effect becomes more and more prominent (Schaefer and Vincent, 1908). Pitressin produces the same effects.

Pitocin produces a transient fall of blood pressure and markedly weakened cardiac contractions, in man and various animals, but has little effect in dogs. The depression of cardiac muscle is direct, not by coronary constriction, as is that of pitressin (R. A. Woodbury *et al.*, 1944).

Howell, 1898, showed that the pressor action is confined to the posterior lobe of the gland. The *hypophyseal portion* lowers the pressure (W. W. Hamburger, 1904, 1910); the *pars intermedia* also produces chiefly a fall, preceded and followed by a rise (Lewis, Miller and Matthews, 1911).

The *rise of pressure* is due solely to vasoconstriction, for the aortic blood flow decreases (Tigerstedt and Airila, 1913), and the organ volume diminishes during the rise, with a few exceptions of passive dilatation (notably the kidneys). The response to depressor stimulation is decreased (Auer and Meltzer, 1913). The vasoconstrictor action is peripheral, for it occurs in perfused organs (Rischbieter, 1913) and in excised arterial segments (Bonis and Susanna; Röthlin, 1921, discusses the variations in different areas), and it can be produced locally by application to the scarified skin (Carrier, 1922). According to Krogh, the muscle fibers on the capillaries are far more sensitive than the arterial muscle, in contrast to epinephrine. The action of pituitary appears to be on the contractile substance rather than on the receptive mechanism; for ergotoxine is not an effective antagonist, and the response of different vessels is not parallel to their sympathetic innervation.

The *fall of blood pressure* on repeated injection of pituitary extract or pitressin is not due to vascular relaxation, for it is not seen in perfusion (McCord, 1911). It is probably due to progressive failure of the heart to withstand the coronary constriction.

This interferes even in the first injection, for the pituitary rise is considerably greater if coronary constriction is prevented by epinephrine or ephedrine (Melville and Stehle, 1931). The fall occurs more readily in cats and rabbits than in dogs (Hamilton, 1912). If the intervals between injections are sufficiently long for the heart to recover, or if only small doses are injected, the response remains uniform (Hoskins and McPeek, 1913), thus permitting the bio-assay of the pressor principle (Hamilton, 1912). With extracts, the depression may be exaggerated by the presence of histamine-like substances (E. Larson, 1931).

Effect in Shock and Collapse.—The pituitary rise of pressure is more pronounced and sustained if the pressure has previously been lowered (as by hemorrhage, destruction of brain and cord, traumatic shock, choline, peritonitis; Mammery and Symes, 1908). Its use was therefore suggested in the treatment of these conditions (Blair Bell, 1911). It would be useless in the disorganization of severe shock, but may have some value in milder collapse (0.3 to 2 cc. of the U.S.P. solution, or half this dosage of pitressin every hour if necessary). Edmunds and Cooper, 1925, found it useful in mild experimental diphtheria toxemia, but less effective than glucose injections. Melville, 1932, found the joint effect of pituitary with epinephrine or ephedrine more potent against the low blood pressure of histamine shock, and the like, than either agent alone.

The superiority of pituitary over epinephrine in histamine shock is probably explained by the more prolonged action; but Krogh attributed it to projection of the constrictor action further along the *capillaries* by participation of the Rouget cells. However, Aschoff considers these as adventitious histiocytes, and not muscular; and J. B. Rogers claims that stimulation of the pericapillary cells does not constrict the capillary lumen, but pulls it outward.

Clinical Cardiovascular Effects.—With normal individuals, intramuscular injection of ordinary doses does not produce any decided change of *blood pressure*, but the skin vessels are contracted, causing marked *pallor* (Moffat, 1933). Grollman and Geiling, 1932, observed no effect from *pitocin; pitressin* caused a decided but brief fall of *pulse rate, cardiac output* and *oxygen consumption*, followed by more prolonged rise. Patients with *essential hypertension* may show a slight fall of systemic and slight rise of diastolic pressure (A. H. Elliott and Nuzum, 1935).

Unanesthetized dogs respond to intravenous injection of the pressor principle by considerable fall of pressure, with slowed heart. Later injections do not cause this acute collapse, and it is antagonized by the oxytocic principle (Melville, 1936). Hypodermic injection is not likely to produce this effect. *The influence of various anesthetics* is reported by Raginsky *et al.*, 1930.

Intravenous injection of pitressin into dogs produces transient increase of blood flow through the *cutaneous vessels*, partly by increased blood pressure, partly by active vasodilatation, for it is diminished by nerve degeneration. It is absent in most rabbits (Woodbury and Ahlquist, 1946).

Cisternal injection of pitressin raises the blood pressure, presumably by direct stimulation of the vasoconstrictor center (Heller and Kusonoki, 1933).

Injection into the third ventricle of 1 to 1.5 cc. of pituitary solution causes severe reactions in human subjects, by acting on the hypothalamic nuclei; if these are inactivated by lesions, responses do not occur, nor in deep avertin anesthesia which depresses the diencephalon (H. Cushing, 1931).

Heart.—The contractions of excised hearts are strengthened by pituitary extracts; but in intact animals the cardiac efficiency is depressed by the diminution of oxygen supply consequent on coronary constriction. The rate is slowed by the pressure reflex.

The *output of the heart* is decreased, regardless of the rate, and the efficiency of both ventricles is diminished so that the pressure in the pulmonary artery falls (Wiggers, 1911), and the vein pressure rises with large doses (Rosenow, 1920). The *portal pressure* is lowered and the portal flow diminished by the constriction of the splanchnic vessels (G. A. Clark, 1928). The *rate of the heart* is generally slowed during the rise, quickened during the fall, of blood pressure (also with pitressin; Gruber and Kountz, 1930); chiefly by pressor reflexes (Beco and Plumier, 1913).

The electrocardiogram of dogs shows characteristic changes of the T wave when the blood pressure falls. If the vagi were divided, the P wave is also reversed. These effects are attributed to anoxia of the myocardium by *coronary constriction* and are prevented by ephedrine. Direct myocardial effects have not been demonstrated even with large doses. Phenobarbital sensitizes to the coronary constriction and disturbs normal ventricular conduction, so that pituitrin may induce ventricular fibrillation in dogs (Melville, 1939). The *coronary flow* is slowed both in systole and diastole, even by small doses (H. D. Green *et al.*, 1942), notwithstanding the rise of aortic pressure (Morawitz and Zahn, 1914). Perfused excised hearts also show the coronary constriction, and slowing of the rate, unless excessive acidity of the extract produces dilatation (L. N. Katz and Lindner, 1939). The *amplitude*, however, is generally increased (Gruber, 1926) unless the extract contains the depressant chloretone (Wiggers, 1911). *Excised frog heart* reacts with greatly increased excursions. The rate is quickened by small doses; large doses slow to final standstill (Einis, 1913). The influence of potassium and calcium ions on the response was studied by DaCosta, 1926. *The coronary vasoconstriction can be antagonized* in perfused hearts by epinephrine, ephedrine, histamine, nitrite or chloretone; and with intact animals, epinephrine and ephedrine potentiate the pressor response to pituitary injection, and diminish the fall (Melville, 1933).

Myocardial Degeneration.—Repeated injection of large doses of pitressin result in histological changes, especially in the subendocardial layer of the left ventricular muscle, resembling those produced by toxic doses of digitalis. *Cellular degeneration* occurs also in the *cerebral cortex* and in the *stomach* (W. H. Dearing *et al.*, 1944).

Antagonism to Acetylcholine.—Pitressin inhibits the depressor effect of acetylcholine, the vagus response and the increase of submaxillary secretion (Necheles and Neuwelt, 1938).

Other Vascular Areas.—The pituitary constriction includes the pulmonary, cerebral and coronary vessels, which respond but poorly to epinephrine. The brain volume, however, may be increased by the high blood pressure (Raphael and Stanton, 1919). Pituitary has little constrictor action on the intrahepatic vessels, but lowers the portal pressure and decreases the portal blood flow by constricting the splanchnic vessels (G. A. Clark, 1928). The vessels of frogs are dilated (Froehlich and Pick, 1913).

Blood Volume and Blood Cells.—During the acute pituitary constrictor action, the effects are as with epinephrine (Brednow, 1931): increase of circulating erythrocytes (CO method) and decrease of plasma volume (dye method). Daily administration of posterior pituitary (as of epinephrine) results in polycythemia even after excision of the spleen, attributed to ischemic stimulation of the bone marrow (J. E. Davis, 1942). Massive doses administered hypodermically to rabbits produce severe macrocytic hyperchromic *anemia* (Dodds and Noble, 1935), due to osmotic hemolysis when the plasma is rendered hypotonic by the retention of water in the oliguric stage (Gilman and Goodman, 1937).

Cerebrospinal Fluid.—Tajitsu, 1929, claimed decreased formation of the fluid. Cow, 1915, believed that the pituitary principle occurs sometimes in the cerebrospinal fluid, especially after injection of extracts of the duodenal mucosa, which he considers as a stimulant of pituitary secretion. Mestrez and Van Caulaert, 1927, confirmed the presence of the oxytocic principle in the fluid obtained from occipital puncture in man as well as in animals; but none was found in the lumbar fluid, suggesting that it passes into the blood from the cerebral ventricles.

Lymph flow decrease was described by Peterson and Hughes, 1924.

Urine Flow.—Injection of pituitary extract produces three successive and unrelated effects: (1) brief *anuria*, of little importance, attributed chiefly to spasm of the ureters (Mackersic, 1925); (2) brief *diuresis*, of little practical importance, by the improved renal circulation, resulting chiefly from passive dilatation of the renal afferent arterioles by the rise of blood pressure, and practically parallel to the latter in degree and duration (ten minutes to an hour); succeeded by (3) *oliguria*, which reaches a maximum in the third hour, and fades by the tenth hour. It is due chiefly, if not entirely, to a direct action on the renal tubules, increasing reabsorption. Glomerular filtration is not increased (T. Bjering, 1934). This results in decreased volume and increased concentration of the urine. It overcompensates for the diuresis, so that the daily urine volume is generally somewhat decreased in normal subjects, but especially if the output was excessive, in polyurias. It is utilized for checking diabetes insipidus. If the water consumption is high, the limitation of excretion results in retention, leading to hydremia and to the nervous symptoms of cerebral edema. All the urinary actions are produced by pitressin; pitocin has practically no effect (Bugbee and Simond, 1928).

Primary Anuria.—Although this is usually attributed to ureteral spasm, it occurs also if the ureter is excluded by catheterization of the renal pelvis (J. B. Ross and Stehle, 1930), so that there must be other factors which have not been explained.

The pituitary polyuria was first described by Schaefer and Herring, 1908, who attributed it to stimulation of the renal cells. This is contradicted by the absence of increased oxygen consumption (Knowlton and Silverman, 1918; Gremels, 1929). The *kidney volume*, which decreases during the primary anuria, increases parallel to the polyuria, and decreases again with the later oliguria (D. D. MacDonald, 1933). Richards and Plant, 1922, also obtained diuresis with diminished renal blood flow, but increased kidney volume; they ascribed this to contraction of the efferent arterioles, which would increase the glomerular filtration pressure. *Direct microscopic observation* in frogs showed dilatation and increased number of functioning glomeruli with small doses, the reverse with large doses (Richards and Schmidt).

The dilator response is mainly passive, *i. e.*, by the increased blood pressure and by the displacement of blood from the splanchnic area, for *perfused kidneys* generally respond by constriction (McCord, 1911; Osaki, 1927), sometimes followed by dilatation. The larger renal arterioles are dilated (Cow). These changes occur also if pituitary is reinjected during the oliguric stage, so that the urine flow is temporarily increased.

The *excretion of solutes* is increased, including the urea and ammonium (Stoland and Korb, 1920), and the inorganic ions (Stehle, 1927). *With rabbits rendered polyuric by the continuous injection of sugar* or by phlorhizin, pituitary extract also causes marked but transient increase of urine flow, with increase of chloride output and decrease of sugar content, consistent with increased glomerular filtration (E. E. Nelson, 1934). *Extrarenal factors* may contribute to the diuresis; this is usually accompanied by hydremia (Underhill and Pack, 1925), which is probably due to mobilization of saline ions, chloride, K, Ca, Mg, and phosphate, of the tissues. The excretion of these is considerably increased, independently of the diuresis and even in its absence (Stehle, 1927); in nephrectomized rabbits, pituitary injection increases the Cl concentration of the blood for some hours (F. Buschke, 1928). Rabbits, however, appear especially subject to chloride mobilization by many agencies.

Pituitary Therapy of Diabetes Insipidus.—The polyuria in the disease is due to defective tubular reabsorption of water. Glomerular filtration is not altered (review, J. P. Peters, 1944). The polydipsia is secondary to the loss of fluid, for nephrectomy abolishes the thirst (H. G. Swann, 1940). Pitressin corrects the condition by increasing tubular reabsorption. Hypodermic injections decrease the volume of urine, increase its specific gravity and the percentage of chloride and nitrogen (M. Rosenfeld, 1940), and greatly diminish the thirst. The dosage ranges from 0.5 cc. of posterior pituitary injection or pitressin solution, every second or third day, to 1 cc. three times daily. The medication must be continued indefinitely.

Intramuscular injection of *pitressin tannate in oil*, 5 pressor units in 1 cc., gives a more lasting effect, checking the polyuria for about forty-eight hours (G. W. Thorn and Stein, 1941). Other channels of administration (oral, rectal, intranasal) may produce some improvement, but are less effective, and generally unreliable (Blumgart, 1922).

Dried posterior pituitary gland may be used as a snuff, 0.15 Gm. per day, divided into two or three doses; or 0.5 cc. of pitressin solution may be sprayed into the nose three times daily, at least to supplement the injections (F. M. Smith, 1934).

The *pituitary oliguria* is due entirely to the pressor fraction. It is produced by posterior pituitary extracts of all vertebrates, including amphibians and fishes; but only mammalian kidneys respond to it, coinciding with the existence of the water-reabsorbing structures, the loops of Henle and the terminal segments of the tubules (review, J. P. Peters, 1944).

The time relations of the decrease of urine volume and increase of concentration were described for *normal human subjects* by Miasi, 1922. The diminution of urine volume is proportional to the previous volume: it may be absent (M. H. Rees, 1918) if the daily output was already small, although pitressin generally causes additional concentration of the urine in dogs, even with restricted water and food intake (W. G. Paine and Nelson, 1939). The decrease of urine volume is large if the subject was polyuric (Brunn, 1920), from high water income, diabetes insipidus (Velden, 1913), or from the administration of urea or mercurial diuretics. These are mutually antagonistic to pituitary (W. Raab, 1929). Insulin is also antagonistic to the pituitary polyuria (Koref and Mautner, 1926).

The *concentration of the urine* is increased, but with urea (Addis *et al.*, 1918), urate (Hammett *et al.*, 1920), phenolsulfonphthalein (Bugbee and Simond, 1928), and doubtless other substances, the concentration is not in proportion to the reduced volume, so that retention results. The transformation of benzoic into *hippuric acid*, in nephritis, is reported to be increased by pituitary, independent of any diuresis (Farini and Ceccaroni, 1915).

Posterior Pituitary Injection is used as a *clinical test of renal concentration*; 1 cc. should raise the specific gravity of the urine to 1.023 or higher (W. A. Sodeman and Engelhardt, 1943).

The diminished excretion of water results in *hydremia* (Brunn, 1920) and *edema*. The *osmotic pressure of the serum* is reduced, so that it may become isotonic with 0.561 per cent NaCl and hemolyze the red cells (Gilman and Goodman, 1936). The *increased water content* is peculiarly distributed: it is marked in the central nervous system (medulla, basal ganglia and cerebrum), and small in the muscle and liver; the skin actually loses water (G. E. Ellerbrook *et al.*, 1930). With high water income, the edema of the nerve centers and increased intracranial pressure result in alarming symptoms of "*water disease*": headache, nausea, asthenia, incoordinated convulsions, coma and sometimes death. Intravenous injection of hypertonic salt solution causes prompt improvement (Rowntree, 1924).

The site of the oliguric action is renal, for heart-lung-kidney preparations also respond by reduced output of urine and increased concentration of urinary chloride (Hemingway and Peterson, 1929). *Denervation* of the kidney does not inhibit the oliguria (Oehme and Oehme, 1918), but there appears to be some central correlation, or posterior pituitary injection fails to inhibit water-ingestion polyuria in man during sleep (Labbé and Azérad, 1926), deep hypnosis, progressive paresis and with some brain tumors.

The renal action is conceived as *increased reabsorption of water* from the tubules. The amount of glomerular filtrate is probably not decreased in mammals. In birds there is some decrease in glomerular filtration by large doses, and this is more marked in reptiles. Amphibians and fish do not respond with oliguria (Burgess *et al.*, 1933). The alternative explanation of *increased water affinity of the tissues*, as advocated especially by Stehle, 1927, appears to be contradicted by the absence of retention when the water income is limited, and by the increased water content of the serum and corpuscles when the water is retained.

Pitressin does not interfere with the *absorption of fluid* from the intestinal tract (review, J. P. Peters, 1944).

The urinary sodium chloride excretion is greatly increased by posterior pituitary injection in rats to which water is administered, by 300 to 600 per cent, when the delay of water excretion is only 40 per cent. If salt is administered. the oliguria is changed to polyuria. The salt phenomenon appears to be due to the Na and not to the Cl ions, for potassium chloride does not have this effect (O. S. Gibbs and Fulghum, 1946). Pituitary diuresis lowers the *halide concentration of the serum*, but does not change the distribution of chloride and bromide between serum and corpuscles (A. R. McIntyre and Van Dyke, 1931).

Normal water regulation is adjusted largely by the release of antidiuretic hormone from the posterior pituitary, under the control of the central nervous system (review, M. Pickford, 1945). The importance of the pituitary regulation is indicated by the observation that the urine of rats on limited water income has a potent antidiuretic effect when injected into normal rats, but much less so if the hypophysis was removed before the water limitation was practiced (Gilman and Goodman, 1937; Boylston and Ivy, 1938).

The oliguria is effected by the total osmotic concentration of the plasma rather than by any individual constituent (G. H. Chambers *et al.*, 1945). It occurs also if the plasma is rendered hypertonic by intravenous injection of concentrated sodium chloride or sulfate or urea solution (K. Hare *et al.*, 1945). This diminishes the store of antidiuretic substance in the posterior pituitary (G. H. Chambers, 1945). Oral administration of concentrated sodium chloride solution produces histologic changes in the posterior pituitary (Selye and Hall, 1943). The suppression of urine flow by certain afferent stimuli appears to be due to pituitary stimulation, since this may be abolished by destruction of the pituitary stalk (Haterius, 1939) or by excision of the posterior pituitary (O'Connor and Verney, 1942).

Cow, 1915, who produced diuresis by the injection of *extracts of duodenal mucosa*, assumed that this is due to stimulation of the pituitary gland, and that *water diuresis* results from absorption of this pituitary stimulant.

Small amounts of *different antidiuretic substance* exist in the blood, urine and cerebrospinal fluid even after excision of the pituitary gland (A. M. Walker, 1939). Extracts of human urine contain substances which have no effect on diuresis when injected alone, but which prolong the diuretic effect of posterior pituitary when both are injected hypodermically into rats (R. L. Noble *et al.*, 1939; N. K. Schaffer *et al.*, 1941). Their behavior resembles that of antidiuretic beef liver extracts (Theobald and White, 1933).

Water-Imbibition of Frogs.—If frogs kept in water are injected with small doses of pituitrin, their weight increases ("*Brunn's reaction*"; about 15 per cent in four hours), and the normal loss of water in dry environment is decreased. This action, however, is not connected with the oliguric action, for in contrast to this, the frog edemic effect is about three times greater with pitocin than with pitressin (Steggerda and Essex, 1934; Oldham, 1936). The imbibition is prevented by the addition of 0.4 per cent NaCl to the water. It is greatest at *p*H 7, but there is little difference between *p*H 6 and 8. The imbibition is twice as great in nonhibernating as in hibernating frogs, probably by relation to the sexual cycle. It is dimnished by anesthetic doses of narcotics, but sedative dosies may increase the uptake (E. M. Boyd *et al.*, 1939). Judging from the difference of dosage, the action is presumed not to be due to any of the known hormones (H. Heller, 1941).

Blood Sugar Level.—The injection of pituitary extract produces considerable glycosuria and hyperglycemia, probably by direct action on the liver, for it occurs also after excision of the suprarenals (Geiling, 1928). La Barre, 1930, claims that the hyperglycemia is not produced after excision of the suprarenals, and therefore attributes it to increase of epinephrine output. It *antagonizes insulin hypoglycemia*, and apparently insulin normally mobilizes a protective pituitary secretion, for removal of the pituitary gland increases the sensitiveness to insulin, and this is antagonized by the injection of pituitary extract (Geiling *et al.*, 1927). The hyperglycemia and the protection against insulin are produced by both pitressin and pitocin, with the distinction that the pitressin rise is accompanied by increase of the plasma phosphate, and oxytocin is not (Geiling, de Lawder and Rosenfeld, 1931).

Other Effects on Metabolism.—Pituitary injection increases the *basal metabolism* of normal individuals, but is said to lower it in hypothyroid patients (McKinay, 1921). Pal, 1917, claimed that in *Basedow's diseasle* it decreased the toxic symptoms and the size of the thyroid. It produces *hyperthermia* in pigeons that were rendered poikilothermic by cerebrothalamic ablation; it has no effect on the temperature of normal pigeons (Rogers, 1921). The *growth* of puppies was improved by the injection of posterior pituitary; feeding of the gland had no effect (Downs, 1927).

Respiration is affected chiefly through the circulatory changes. In unanesthetized animals it is generally quickened, with interspersed periods of apnea. With intravenous injection during anesthesia, Paukow, 1912, described primary arrest during the fall of pressure, then an increase and a second stoppage during the rise. Nice *et al.*, 1914, described the characteristic effects as primary increase of depth, followed by shallow and generally slow, but sometimes quickened, respiration. These disturbances set in with the circulatory changes, but are not so lasting. They fail to occur after a few injections have been made. In frogs, tadpoles and fish the center is paralyzed (Hepner, 1915).

Bronchial Muscle and Asthma.—Pituitrin has little if any effect even in large doses (Jackson and Mills, 1919; S. Okada, 1940). Earlier reports of bronchial spasm were probably due to contamination with histamine.

The smooth muscle of *necturus lung* is not constricted by pituitary or by barium (Luckhardt and Carlson, 1921).

Milk.—Injection of posterior pituitary extract into goats increases the yield at the next milking by more complete expression of the stored milk, through contraction of the smooth muscle of the mammary gland. The yield at the next following milking is correspondingly decreased, the daily yield being unchanged (Simpson and Hill, 1914; Gaines, 1915). The response is lost in the later months of lactation (Röthlin *et al.*, 1922). It is absent in cows (J. C. Shaw, 1942) and generally in women; but Hill and Simpson, 1914, reported marked increase of milk volume and fat after injection of 1 cc. of the solution in the fifth month of lactation.

Iris.—Contradictory results have been reported (Pollock, 1920).

Paramecium.—Pituitary extract increases the pulsation frequency of the contractile vacuole.

Melanophores.—The skin of frogs and other amphibians appears darker after the injection of pituitary extract or on immersion of the excised skin, through expansion of the melanophore cells; removal of the hypophysis results in blanching. The melanophores of fish fundulus do not respond to pituitary, although they are contracted by epinephrine. Those of the minnow (phoxinus levis) respond actively. The melanophore principle, intermedin, is formed in the intermediate lobe and is distinct from the pressor and oxytocic fractions (Dryer and Clark; Zondek, 1934; Geiling *et al.*, 1936). It accelerates the oxidase system tyrosine: tyrosinase, which is inhibited by the pressor and perhaps by the oxytocic principle (Fostvedt, 1939). Extracts of other tissues, and histamine, are ineffective (Hogben and Winton, 1922). Apparently identical effects are produced by the chromatophore hormone of the crustacean eyestalk (Abramowitz, 1938).

Toxic Actions.—Aside from the accidents arising from actions on smooth muscle, such as rupture of the uterus or asphyxiation of the fetus, toxic effects are rare and generally unimportant. Tinnitus, anxiety, albuminuria, unconsciousness, eclamptic attacks, mydriasis, amaurosis, diarrhea have been reported.

Anaphylactoid reactions, urticaria, angioneurotic edema, dyspnea, and the like, occur occasionally, but are uncommon (F. A. Simon and Ryder, 1936; Abbett, 1940).

Contraindications: Epilepsy, hypertension, coronary disease and pregnancy are listed.

Standardization of pituitary extracts is essential because of the serious consequence of overdosage, especially in obstetrics. Since chemical assay is not feasible, it is necessary to measure the potency by the effects. The comparison of the response of the excised uterus of guinea pigs with a standard sample of dried pituitary has the advantage that it measures the action that is most likely to become dangerous (Burn and Dale, 1922). Details described in the U.S.P. must be meticulously observed.

The effects on the blood pressure go fairly parallel. Indeed, the activity of the fresh gland is remarkably constant as to pressor and oxytocic properties, and their ratio to each other. The *pressor assay* is described by Hamilton and Rowe, 1917; the assay of antidiuretic action by G. C. Ham, 1943.

Preparations.—***Posterior Pituitary Injection,** U.S.P., *Posterior Pituitary Solution; Pitressin*, a sterile solution in water for injection, prepared from the posterior pituitary lobe of "domestic animals used for food by man," adjusted by bio-assay on excised uterus of guinea pigs, in comparison with the U.S.P. Reference Standard, so that 0.1 cc. has the oxytocic activity of one U.S.P. Posterior Pituitary Unit, identical with one International Unit, or 0.5 mg. of the Reference Standard Pituitary Powder. Some brands are preserved with chloretone. Dose, hypodermically, 2 to 10 units (0.2 to 1 cc.). Usually available as 5 units in 0.5 cc. and 10 units in 1 cc. A solution of double the official strength was marketed as "Surgical Solution." *Pitocin*, N.N.R., is an aqueous solution of the oxytocic fraction, standardized to correspond to the oxytocic activity of the U.S.P. Posterior Pituitary Injection. *Pitressin*, N.N.R., is an aqueous solution of the pressor-diuretic-oliguric fraction, standardized to contain 20 "pressor units" per cubic centimeter, double the pressor activity of Posterior Pituitary Injection. Dose, 0.3 to 1 cc. intramuscularly. *Pitressin Tannate in Oil*, N.N.R., is a suspension corresponding to 0.5 mg. of standard posterior pituitary powder (5 pressor units) per cubic centimeter. Used for prolonged action, 0.3 to 1 cc. intramuscularly (never intravenously) every thirty-six to forty-eight hours. Available in ampuls of 1 cc.

ERGOT AND ITS ALKALOIDS

Ergot (Secale cornutum) is a fungus (Claviceps purpurea) growing in the grain of cereals; the official is obtained from rye. The fungus goes through several stages of development, the resting stage (sclerotium) constituting the drug. It is used to contract the uterus (by peripheral action) and thus check postpartum hemorrhage. It also stimulates other forms of unstriped muscle, especially the intestine and blood vessels. The consumption of grain infested with ergot leads to gangrene and spasmodic effects. Epidemics of "ergotism" were formerly frequent and must have occurred in antiquity, although the causal connection was not recognized. It is rare in civilized countries, since the ergot is removed by the modern methods of treating the grain. The oxytocic effect was learned from midwives and was first mentioned in Lonicer's Kräuterbuch of 1565. Its use in regular medicine dates practically from Stearns, 1807 (N. Y. Med. Repository). Aside from its uterine action, ergot produces abolition of response to augmentory sympathetic stimulation; rise and fall of blood pressure; cyanotic stasis and gangrène and other effects. Their complexity is due partly to the multiplicity of active constitutents, which vary in different specimens, but each of the pure principles also has several apparently unrelated actions.

The **constituents** fall into the following groups: (1) *Alkaloids:* These are responsible for the characteristic actions of ergot. They include: (*a*) The active ergotoxine and ergotamine and their inactive isomers ergotinine and ergotaminine. The minor alkaloids *ergosine* and *ergocristine* have essentially identical actions. (*b*) The active ergonovine (with various synonyms), and its inactive isomer ergometrinine. (2) *Amines:* (*a*) Histamine (misnamed ergotidine and ergamine). (*b*) Tyramine (misnamed ergamine and uteramine). (*c*) Other aromatic amines (Engeland and Kutscher, 1910). (3) *Acetylcholine*, also choline and betaïne. Ergothione is a betaine of thiohistidine (Barger and Ewins, 1911). (4) *Ergosterol*, inactive in itself and not absorbed, but yields viosterol on artificial irradiation. (5) *Ergotinic acid*, a sapotoxin with the actions typical of that group. (6) *Miscellaneous constituents: Sclererythrin*, a red pigment which serves as a test of the presence of ergot in bread; resinous acids, some peculiar sugars, fat (some 35 per cent) and others. The nonalkaloidal constituents are further discussed in other sections (see Index).

All the ergot alkaloids are related chemically as well as in their actions. They are derived from lysergic acid which contains an indole group (W. A. Jacobs and Craig, 1935; S. Smith and Timmis; review, G. Barger, 1938). A synthetic hydroxybutylamide of lysergic acid, "*methergine*," synthesized by Stoll and Hofmann, 1943, has the typical ergonovine action (Kirchhoff and Wilson, 1944) and may be used in the third stage of labor, 0.2 mg. hypodermically or by vein (P. C. Roberts, 1944). The isolation offered unusual difficulties. The active alkaloids are unstable and change easily into their more stable inactive isomers. Oxygen and especially light transform them into dark-colored products of feeble activity. They tend to fix organic solvents in their molecule, analogous to water of crystallization, and this gave rise to misleading statements of elementary composition. Only small amounts are present in ergot, sometimes almost none, especially if it has been exposed to dampness. The constituents vary with different lots of the drug. One or the other alkaloid may be practically absent. Russian ergot contains only ergotamine; Spanish and Portuguese yield little ergotoxine and ergonovine. It is still doubtful whether all the alkaloids have been isolated (Stoll, 1936).

The chemical history of ergot is confused by the unsuccessful investigations and by the multiplication of names for products which later work showed to be impure, or identical with others. The *literature* of the ergot components is reviewed by E. E. Nelson and Calvery, 1938.

Historical on Ergotinine, Ergotoxine and Ergotamine.—Tanret, 1875 to 1879, isolated a crystalline alkaloid, which he named *ergotinine*, and which is the practically inactive isomer of ergotoxine (Kraft, 1906). It is still designated by this name. Tanret also isolated ergosterol and a noncrystallizable alkaloidal fraction, "ergotinine amorphe," and from this Barger, Carr and Dale, 1907, isolated amorphous *ergotoxine* and its crystalline phosphate, and showed its pharmacologic actions. Kraft, 1906, arrived independently at the same results. Crystallized ergotoxine was prepared by S. Smith and Timmis, 1930. *Ergotamine* (Gynergen) was isolated and crystallized by Stoll from certain kinds of ergot, and shown to be closely related to ergotoxine (Dale and Spiro, 1922), but not identical with it (Smith and Timmis). It is convertible into the feebly active ergotaminine (Stoll, 1936).

Historical on Ergonovine.—Alcoholic preparations of ergot, as those of the U.S.P., contain the ergotoxine and ergotamine, but these alkaloids do not pass into watery preparations, as those of the B.P., although these are actively oxytocic. Indeed, the original use of ergot by J. Stearns was based on a watery decoction (half a drachm of powdered ergot boiled with half a pint of water and administered in three doses at twenty minute intervals). Evidently, therefore, these alkaloids do not fully represent the oxytocic activity. Barger, Dale and Dixon, 1909, suggested that the activity of the water extracts is due to histamine and tyramine; but these are not very active by mouth and were not found satisfactory clinically. Clinical demonstration of oxytocic activity, however, was not satisfactory until Moir, 1932, proved the activity of extracts supposedly free from known alkaloids, on the postpartum human uterus, with a graphic method. This served as a starting point for further investigations by Dudley and Moir. In March, 1935, they described a crystalline alkaloid which they considered chiefly responsible for the oxytocic action of ergot, and therefore named it "*ergometrine*" (Dale, 1935). Several other investigators in the meantime had worked independently on the same problem and announced the discovery of this alkaloid practically simultaneously. M. R. Thompson, 1935, claimed to have described its isolation in 1932 and to have crystallized it in 1934, naming it first "X alkaloid," and then "*ergostetrine*." His work was not altogether clear and had been described chiefly in an unpublished thesis. Kharash and Legault announced the alkaloid as "*ergotocine*" in November, 1934, and published clinical data in 1935. This is marketed as "*ergotrate*." Stoll and Burckhardt, 1935, had isolated pure crystals of the alkaloid, but had not investigated its actions. Stoll, 1935, claimed that his is the first description of the pure substance. The identity of these alkaloids has been conceded to their discoverers (Science, 1936, *83:* 206). The question of priority depends upon the point of view. As none of the names complied with the rules of N.N.R., the Council felt compelled to coin an independent name "ergonovine" (J.A.M.A., 1936, *106:* 1008). The *literature* of ergonovine is reviewed by R. G. Smith, 1938.

Impure Principles.—These are still important for understanding the older literature. They are classified by Barger and Dale as follows, in chronological order:

Wenzell, 1864: *Ecboline and Ergotine* = mixtures of the alkaloids, containing choline (Meulenhoff, 1899).
Tanret, 1875: *Amorphous Ergotinine* = impure mixture of ergotinine and ergotoxine.
Dragendorff, 1877: *Picrosclerotine* = ergotinine, possibly mixed with some ergotoxine.
Podwyssotski, 1883: *Sclerocrystalline* = ergotinine.

Kobert, 1884: *Sphacelinic Acid* = inactive resin with adherent alkaloids.

Cornutine = alkaloidal resin, probably containing some ergotoxine and perhaps some active alkaloidal decomposition products.

Ergotinic Acid = a sapotoxin.

Keller, 1896: *Cornutine* = impure mixture of ergotinine with ergotoxine.

Jacobj, 1897: *Chrysotoxin* = inactive yellow coloring matter with small porportion of adherent alkaloid.

Secalintoxin = mixture of ergotinine and ergotoxine.

Sphacelotoxin = impure ergotoxine.

Secalin = impure ergotinine.

Kraft, 1906: *Hydroergotinine* = synonym for ergotoxine.

Vahlen, 1906 and 1908: *Clavin* = inactive mixture, consisting of nearly equal parts of leucine, isoleucine and valine (Van Slyke, 1909).

Marino-Zuco and Pasquero, 1911: *Clavisepin:* claimed to be an active glucoside; not confirmed.

Ergoclavine of Kussner and *Sensibamine* of Wolf are probably mixtures of the ergotamine group (Stoll, 1935).

Ergotine is a name applied to a variety of pharmaceutic extracts.

Characteristics of the Ergotoxine and Ergotamine Group.—The alkaloids *ergotoxine* (Barger, Carr and Dale, 1906; *hydroergotinine*, Kraft, 1906) and *ergotamine* (Stoll; marketed as tartrate under the name "Gynergen") are closely related chemically, and practically indistinguishable pharmacologically; their threshold concentration for direct stimulation, and for inhibition of the epinephrine stimulation of the excised uterus (Dale and Spiro, 1922), is the same; but ergotoxine is nearly twice as potent as ergotamine in the pyrogenic, convulsive and lethal dosage for rabbits (Lozinski, Holden and Diver, 1931; Rothlin, 1932, 1935). One or the other predominates in different specimens of ergot. Both give the color reaction of ergot. They form colloidal solutions in water, and are easily precipitated by salts and acids. They do not therefore pass readily into watery extracts of ergot, but these may contain the ergonovine alkaloids. Alcoholic extracts contain both groups of alkaloids. Ergotoxine is easily changed into its isomer *Ergotinine*, and Ergotamime into its isomer *Ergotaminine*, which are pharmacologically almost inactive. The ergotoxine and ergotamine are actively oxytocic, but clinically inferior to ergonovine. They produce the cock's comb cyanosis and grangrene effects. They are responsible for the sympatheticolytic action (epinephrine reversal, Dale, 1905), and are chiefly concerned in the stimulation of the uterus, the vasoconstriction, the bronchial constriction, the intestinal irritation and the gangrene. (Table and bibliography in Bacq, 1934.) Ergotamine relieves migraine.

Characteristics of Ergonovine.—This has about half the molecular weight of the ergotoxine group. It is the most potent oxytocic constituent of ergot (about twice as potent as ergotamine), and is chiefly responsible for the activity of the aqueous preparations, but is present only in small amount. Its other pharmacologic actions are similar to those of ergotoxine, but generally weaker. It has little sympatheticolytic action. It forms an inactive isomer, ergometrinine (Smith and Timmis, 1935). The free alkaloid is somewhat soluble in water, with strongly alkaline reaction; the salts are freely soluble. It is levoratatory, and gives the color reactions of the ergot alkaloids.

Pharmacologic Actions of Ergonovine.—These include the muscular stimulation of the uterus; evanescent cyanosis of the cock's comb, not proceeding to gangrene; rather slight sympatheticolytic action (epinephrine reversal) on several organs, often obscured and complicated by other effects; slight rise of blood pressure, varying with conditions; depression of frog heart; mydriasis in rabbits; central excitation with general sympathetic excitement and rise of temperature in toxic doses, similar to ergotoxine. The fatal dose is higher than for ergotoxine (G. L. Brown and Dale, 1935; Rothlin, 1935; M. E. Davis, Adair and Pearl, 1936).

Uterine Actions of Ergot Preparations.—In labor, ordinary doses improve the uterine tone, and collect small irregular and noneffective pains into larger effective contractions. Excessive doses produce prolonged tonic contraction (Sharp, 1911). These effects have also been observed directly through a celluloid window inserted in the abdomen of animals (Ludwig and Lenz, 1923). The effects can be produced clinically by the pharmaceutical preparations; or by ergonovine, orally or by injection; or less satisfactorily by injection of ergotamine or ergotoxine. The fluidextract by mouth or rectum is the most economical and accomplishes the full results, unless promptness of action is imperative. Its taste is the chief objection.

The most extensive use of ergot is *after* the delivery, to hasten and sustain the normal retraction, thus obliterating the open sinuses, and checking *postpartum hemorrhage.* When proper doses are used during labor, with the os fully dilated, and no obstruction, they tend to *hasten normal delivery.* Really effective doses, however, are rather dangerous to mother and child. The firm contraction may hinder delivery, and compress and asphyxiate the fetus; rupture of the uterus has been reported; but these accidents are rare. In *early pregnancy*, its effects are much less certain. Contrary to popular opinion, it is not abortifacient unless dangerous doses are long continued. Ergot has also been used in other forms of *uterine hemorrhage* and in chronic metritis, but it has probably little value apart from obstetric conditions.

The relative uterine activity of the ergot alkaloids ranks as follows, in rabbits, taking ergotamine as the unit (Rothlin, 1936): *Tonus augmentation in situ:* ergonovine = 2; ergotamine = 1; ergotoxine = $\frac{1}{2}$. *Epinephrine reversal* on excised uterus: ergotamine and ergotoxine = 1; ergotaminine = $\frac{1}{5}$; ergotinine = $\frac{1}{100}$; ergonovine = less than $\frac{1}{400}$.

Mechanism of Uterine Action.—The action is peripheral, since it occurs also in the excised uterus (Fellner, 1906; human, Rübsamen and Kligermann, 1912). It is directly muscular: the sympatheticolytic action requires much larger doses. La Torre, 1912, found histologic changes in the uteri of dogs treated with ergot. *Calcium excess*, which depresses the tone of the virgin guinea pig uterus, increases the response to the contractor action of ergot (M. Chio, 1922).

Administration of the Pharmaceutical Preparations.—The usual *dosage* is 2 to 5 cc., ½ to 1 drachm, of the U.S.P. Fluidextract. Rectal administration also gives good and prompt effects, and is not especially irritating. The official preparations are quite irritant hypodermically or intramuscularly. The response to ergot taken by mouth or rectum appears in fifteen to thirty minutes and lasts half an hour (L. J. Jones and Barlow, 1934). Opium delays but prolongs the effects; moderate chloroform anesthesia does not modify them (Sharp).

The Liquid Extract of the B.P., an aqueous preparation, merely preserved with alcohol, causes prompt contraction of the human postpartum uterus, on oral administration (Moir, 1932), in doses of 0.6 to 1.2 cc., 10 to 20 minims. Its activity is probably about half that of the U.S.P. fluidextract (Jones and Barlow, 1934). *Commercial aqueous preparations for hypodermic injection* are more or less purified aqueous solutions. They are of uncertain activity (E. E. Nelson and Page, 1928).

Ergonovine (*Ergotrate*) is probably the chief oxytocic constituent of the U.S.P. fluidextract, and exclusively for the B.P. liquid extract. It can be injected intravenously or hypodermically, but acts promptly by oral administration. It produces practically no nausea or other side effects. Its chief limitation is its scarcity and cost. Watery solutions of some of the commercial brands deteriorate rather rapidly.

The clinical dosage of ergonovine by mouth is 0.2 to 0.5 mg., generally 0.3 mg. (or 0.4 of the commercial "Ergotrate"); the intravenous dosage is 0.1 mg. With oral administration, postpartum uterine stimulation begins in five to eight minutes, the full effect is reached in fifteen to thirty minutes and persists for three to four hours, and some contracture remains for five to seven hours or longer. Vomiting does not occur even with three or four times the clinical dosage, in contrast to ergotamine, but with the dosage of 0.5 mg., the uterine contracture becomes painful (Barlow, 1936). In prolonged postpartum bleeding, the dosage of ergonovine may be administered three times daily for several days (M. E. Davis *et al.*, 1936).

Regarding the *scarcity* of ergonovine, Stoll, 1936, stated that the richest source, Spanish ergot, never yields more than 60 mg. of this alkaloid per Kg. Portuguese ergot yields less, and none can be obtained from Polish and Russian ergot. On the other hand, good ergots yield 2 Gm. of the ergotamine and ergotoxine group per Kg. The small yield and limited source of ergonovine would be inadequate for medical use, if this employed ergonovine exclusively.

Ergotamine (*gynergen*) *and ergotoxine as oxytocics* produce the same effects as ergonovine, and the isolated alkaloids can be used clinically, but they are not very satisfactory (Sharp, 1920). Moderate doses (¼ mg. of ergotamine tartrate intramuscularly, 1 mg. orally) are generally ineffective; even 2 to 4 mg. by mouth are not always effectively oxytocic; and with ¾ to 1 mg. there is generally marked nausea and often emesis. The clinical oxytocic action sets in rather slowly, fifteen to twenty minutes after intramuscular injection; the full effect is reached in thirty to forty minutes and persists for an hour or two (Bourne and Burn, 1927).

Other Ergot Constituents on Postpartum Uterine Contractions.—These have practically no share in the oxyttocic action of ergot. *Histamine*, however, to 1 mg. hypodermically, produces uterine contractions in one or two minutes and tonic spasm lasting half an hour (Jones and Barlow, 1936). Its side actions make it undesirable, especially the vasodilatation and the tachycardia. *Tyramine* has little effect on the uterus and is not used clinically.

Ergotamine against migraine is remarkably effective for symptomatic relief. The hypodermic injection generally arrests the migraine attack (in 90 per cent) within an hour; the patient feels weak, generally strongly nauseated, sleeps, and awakens without the migraine, while an untreated attack usually lasts eighteen to twenty-four hours. It does not lose its efficiency with continued use. The best results are obtained if it is administered with the first warning of the impending attack and smaller doses may then suffice. Oral administration may be tried, but larger doses must be used, and it often fails, because it is not absorbed in time. It was feared that continued use would lead to gangrene, but this has not occurred in the many patients who have used large numbers of injections, if the dosage was kept within the ordinary limits, and if the special contraindications were avoided (see below). The injections do not cause material local irritation. *The mechanism of the relief* is obscure. It is not produced by other nauseants, and ergotamine is not effective against other headaches or pains. Ergonovine is considerably less effective than ergotamine intramuscularly, but it is more effective by mouth (Lennox, 1938). The ergotamine treatment was apparently first described by H. W. Maier, 1926 (Lennox and von Storck, 1935).

The *dosage* should start with the hypodermic injection of 0.25 mg. of ergotamine tartrate (gynergen), repeated in two or three hours if necessary; in that case, 0.5 mg. would be injected at once in future attacks; or half this dose may be given by vein. The sublingual administration requires 3 to 4 mg. at the start, followed if necessary by 1 to 2 mg. every hour, not exceeding the total of 10 mg. The oral dosage is 4 to 5 mg. at the start, and if necessary 2 mg. every hour, not to exceed 11 mg. (von Storch, 1938). *The treatment must not be used oftener than twice in a week.* The dose should be kept as small as possible; many patients require less as their condition improves.

Untoward effects are common, but not serious. They are greatest with intravenous injection and least with oral administration. They comprise, in order of frequency: fatigue, nausea, emesis (half of the patients vomit), tingling in hands and feet, muscle pains and stiffness, constricting sensation in throat. Muscular soreness in the thighs was experienced by eight of eleven normal persons taking a 2 mg. tablet by mouth three times daily for twelve to fourteen days (Grinker and Spivey, 1945).

Most of these side actions may be relieved by atropine, 0.4 to 0.5 mg.; the muscle pain and stiffness, by calcium gluconate intravenously, and massage (O'Sullivan, 1936; von Storch, 1938). Tingling, numbness, cold and cyanosis suggest vascular spasm and may be a warning of ergotism. If they recur persistently, the ergotamine should be discontinued for a time; also with substernal pain, until coronary disease is excluded.

The cases of serious sequels, including gangrene, are reviewed by von Storch, 1938. None of these occurred from the administration in migraine, although it has been used by many thousands of patients, up to 24 to 45 mg. per month for five years. The majority of the gangrene cases involved sepsis or obliterative vascular disease, especially coronary. These are *contraindications.*

Carotid Sinus Reflexes.—Ergotamine reinforces the cardiac-inhibiting reflex, but suppresses the reflex changes of the vessels (Heymans and Regnier, 1929). This may perhaps explain the effect on migraine. The *cerebral circulation* in unanesthetized human subjects is moderately increased, probably secondary to the rise of blood pressure, but the increase during migraine headache was not sufficient to explain the relief (W. G. Lennox *et al.*, 1935).

Inefficiency in Related Conditions.—Ergotamine is generally ineffective against *nonmigraine headaches* (Lennox *et al.*, 1936) and quite ineffective in *epilepsy* (continuous oral administration; Loscalzo, 1937).

Dihydroergotamine ("DHE 45") is reported to be as effective as ergotamine against migraine, without producing the untoward effects. It prevents cyclo-propane-epinephrine fibrillation, but does not reverse the epinephrine blood pressure rise (O. S. Orth, 1946). It may be used in pregnancy (M. M. Hartman, 1945).

Ergot as General Styptic.—The efficiency of ergot in postpartum hemorrhage and the vasoconstriction observed in animal experiments led to its use against hemorrhage in other situations. However, as ordinarily administered, it does not affect the blood vessels or blood pressure. Its use is therefore irrational (Bradford and Dean, 1894). It is also useless in pulmonary hemorrhage (Frey, 1909). It has been praised rather uncritically in a great variety of other conditions, which it would be useless to enumerate.

Blood Pressure.—This is practically unchanged by ergot, in man (Sharp, 1911) or animals, unless the ergot is injected into a vein. This produces considerable, but inconstant and complex, changes. The variability is largely explained by the conflicting actions of the different constituents, and by dosage and other conditions.

Sometimes there is a large but brief fall from direct cardiac depression, followed by a slight but prolonged rise from direct cardiac and vascular stimulation (Sollmann and Brown, 1905). The fall is presumably due to histamine and acetylcholine; the rise to ergotoxine or ergotamine and tyramine. Other experiments show little fall and somewhat greater rise (Edmunds and Hale, 1911). This rise is greater if the vasomotor center has been destroyed, and is therefore due to a direct peripheral action on the vessels (Wood and Hofer, 1910). Excised arteries (except the pulmonary) are also constricted (Cow, 1911). The vasoconstriction occurs also in calcium-free solutions (Pearce, 1913). The vasomotor center is not affected by ergot or ergotoxine (Pilcher and Sollmann, 1915). In *experimental hypertension*, produced by raising the intracranial pressure by cisternal injection of saline or kaolin suspensions, ergotamine causes transient lowering of the high blood pressure (C. Lindauer *et al.*, 1938). The pressure in the *pulmonary artery* is increased, whether the carotid pressure is rising or falling (Wood, 1911). Mellin, 1904, Plumier, 1905, and Anderes, 1915, attribute the rise to constriction of the pulmonary vessels. The *coronary vessels* are constricted by ergotamine (L. N. Katz and Lindner, 1939). *Very large doses* of ergot paralyze the vagus center and the vasomotor endings.

The rise of blood pressure with ergotoxine or ergotamine is vascular (diminished organ volume). The constrictor action is exerted directly on the arteries, for it occurs after the medulla has been divided and the vascular ganglia have been excised or paralyzed by nicotine. *Ergonovine* tends to raise the blood pressure slightly, but may lower it in anesthesia. It constricts the vessels of the perfused frog leg (Davis, Adair and Pearl, 1936).

Sympatholytic Action of Ergotoxine and Ergotamine; Epinephrine Reversal.—If a large dose of ergotoxine or ergotamine is injected, and if during the rise of blood pressure the vasoconstrictor nerves are stimulated, electrically, or by epinephrine or nicotine, a *fall* of pressure results, instead of the customary rise. The ergot alkaloid has therefore paralyzed the peripheral sympathetic vasoconstrictor mechanism, leaving the central dilator mechanism active. This *vasomotor reversal* is obtained in pithed cats by 0.5 mg. per kilogram, intravenously. Since ergot itself and barium are still capable of producing vasoconstriction, the arterial muscle can not be paralyzed; and the constrictor paralysis would be referred to the receptive mechanism (Dale, 1905; Sollmann and Brown, 1905). Very large doses finally paralyze the muscle fiber. The antagonism of ergotoxine and epinephrine can also be demonstrated on excised arteries (Macht, 1915) and on the *stomach* (M. Smith, 1918).

The sympatholytic action is especially strong for blood pressure, so that this may be used for the bio-assay of these alkaloids (the Broom-Clark method). It affects also other functions with sympathetic innervation, especially if this is augmentory (for instance, melanophores of fish) (Spaeth and Barbour, 1917), and it also involves some depressant sympathetic innervations (Rothlin). It may be emphasized that it is *not* the most prominent effect of ergotoxine or ergotamine: it requires considerably larger doses than the muscular stimulation and lasts only a few minutes (Polak, 1926). It has been suggested that the phenomenon is due merely to the refractoriness of the high muscular tonus induced by ergotoxine, toward further stimuli. C. W. Darrow, 1943, assumes cholinergic actions. The *central actions of epinephrine, f. i.*, the fever, are not antagonized by ergotoxine (Cloetta and Waser, 1915).

Heart.—The effects of ordinary doses of ergot on mammalian hearts are slight and mainly consequences of the vascular changes; the amplitude is first diminished, then increased. After repeated injections, the heart becomes slowed by a direct muscular action, for the slowing occurs even after atropine. In perfused mammalian heart, Wiggers, 1911, observed diminished systolic contraction and increased tone with decreased amplitude and output.

Ergotamine and ergotoxine increase the excitability of the vagus to electric stimulation and to acetylcholine (Henrijean and Waucomont, 1930). They slow the sinus rhythm and depress auriculoventricular and intra-auricular conduction (Andrus and Martin, 1927). In mammals they have little effect on the response to accelerator stimulation, even with doses a hundred times greater than those that suppress the vasoconstrictor response to epinephrine (H. L. Otto, 1928); but in frogs ergotoxine abolishes the response to accelerator stimulation and diminishes the inhibition on vagus stimulation. Excessive doses arrest the heart; this may be antagonized by atropine, camphor, epinephrine and caffeine, but not by accelerator stimulation (Langecker, 1925). *Ergonovine* is somewhat depressant to the frog heart (Davis *et al.*, 1935).

Ergotamine against Tachycardia of Thyrotoxicosis.—The drug is reported to be effective against the operative tachycardia in these patients, presumably by counteracting epinephrine. It has little or no effect on the other thyroid symptoms, nor does it diminish anoxic tachycardia in normal individuals (Brace and Reid, 1939). In paroxysmal tachycardia, intravenous injection of 0.5 mg. of ergotamine tartrate often returns the heart rate to normal within eight minutes, without untoward effects (E. I. Evans, 1940).

Cyanosis of the Comb of the Fowl.—When ergot preparations are administered to roosters, the tips of the comb and wattles become blue and cold. The effect, which may be preceded by temporary blanching, is perceptible in about half an hour and lasts several hours. This reaction is used for testing the quality of ergot. It is due to the ergot alkaloids, ergonovine being somewhat more potent than ergotoxine and ergotamine (Davis, Adair *et al.*, 1935); histamine produces a similar but much prompter effect (Crawford, 1913); tyramine is ineffective. These changes are probably due to injury of the capillary endothelium, producing vascular stasis.

They are not due to vasoconstriction, for the cyanosis does not occur after other vasoconstrictor drugs; while it is produced by paraldehyde, which lowers blood pressure (Crawford), by cantharidin (Ellinger, 1908), which injures capillaries; and by other drugs which cause vascular injury (large hypodermic doses of cane sugar, piperazine, chromic acid, and the like).

The gangrene action is a characteristic feature of chronic ergot poisoning in man and in many animals. It is readily studied in roosters. It is due to endothelial injury (T. Lewis, 1935), obliterative endarteritis (Kaunitz, 1931), and conglutination thrombosis (W. Jacobj, 1924), analogous to frost-bite (L. Davis *et al.*, 1943; K. Lange, Boyd and Loewe, 1945). The cyanosis of cock's comb is an initial stage of the process. It is produced by ergotoxine and ergotamine. It has followed the therapeutic use of ergot (Caffier, 1927) and of ergotamine, but the latter only if the arterial disease already existed, or in sepsis, or with gross overdosage (critical review, von Storch, 1938). The action of ergonovine does not appear to progress to gangrene (Davis, Adair *et al.*, 1935).

If ergot is given repeatedly to roosters, the bluing persists in the tips of the comb, and gradually involves the entire comb and the wattles. Eventually, these appendages undergo gangrene and may drop off. The extremities may also be involved; in one experiment, the entire wing fell off after a few days.

Histologic Changes.—Von Recklinghausen, 1883, showed that the larger arteries, but not the veins, of the gangrened comb are occluded by hyaline thrombi. The capillaries are congested with red corpuscles. These results were confirmed by Grünfeld, 1890, who gives a good description with colored illustrations. Krysynski observed similar formation of thrombi in a variety of conditions; it is probably the result of a toxic effect on vascular endothelium. No histologic changes are found in the acute cyanosis.

Susceptibility of Different Animals to Gangrene.—Man is quite subject to the gangrene, which begins in the extremities. The fingers, toes, or an entire member may slough off. Pigs react especially by pustular eruptions on the skin; the ears are particularly susceptible. *Horses and cattle* show similar changes. *Dogs and rabbits* do not seem to be susceptible to this action. Bilateral lumbar sympathectomy renders rats more subject to tail gangrene from ergotamine poisoning (Griffith, Comroe and Zinn, 1939). The cause of the varying susceptibility has not been demonstrated. The gangrene always begins in those situations in which the circulation is weakest. It differs in no essential from gangrene produced by any other cause. It may be dry or wet, according to whether liquefying bacteria are absent or present. Salant and Hecht, 1914, describe a *habituation tolerance* to the action of ergot on the cock's comb and to the fatal dose.

Alimentary Canal.—Ergot (2 cc. of fluidextract) and ergotamine (1 mg. by mouth) delay the emptying of the human stomach, averaging 30 and 16 per cent respectively, presumably by direct depression of the gastric muscle (Van Liere and Sleeth, 1939). Intravenous injection of 0.5 mg. of ergotamine tartrate, in man, produces emesis in a few minutes, probably by stimulation of medullary centers; it may be prevented by morphine. Large doses of ergotamine, 2.5 to 3 mg., do not cause vomiting, but protect against apomorphine emesis (S. I. Evans, 1940). Injection of ergot, ergotamine or ergotoxine (10 mg. for rabbits, intravenously) results in marked *increase of peristalsis through the whole alimentary tract.* The sensitiveness to distention is increased (Planelles, 1924), as is also the intestinal motor response to vagus stimulation (Meltzer and Githens, 1916). This produces violent diarrhea and vomiting. The *emesis*, however, is largely central (Eggleston and Hatcher, 1915). The emetic action on pigeons may be used for the bio-assay (C. C. Lieb and Mulinos, 1934). It is a prominent side action in the clinical use of ergotamine. *Ergonovine* is not nauseant clinically and relaxes the intestinal tonus in rabbits (M. S. Davis *et al.*, 1936).

In chronic poisoning, these direct effects are aggravated by vascular stasis, advanced cases showing ecchymosis and ulcer formation. The ulcers involve particularly the lymph follicles, in which the blood supply is poorest. The stasis may lead to effusion of blood into the lumen of the intestine. The appetite is lost. This action on the alimentary canal is also most marked in the animals mentioned, but occurs in others. The *liver* of roosters shows peculiar degenerations, resembling amyloid.

Iris.—Small doses of *ergotamine or ergotoxine* cause mydriasis, probably by sympathetic stimulation. It is increased by excision of the sympathetic ganglion and antagonized by physostigmine. With larger doses, this is followed by miosis (Zunz, 1924). Local application or intra-ocular injection produces mydriasis in guinea pigs, but cats respond by extreme miosis (Koppanyi, 1930). The tonus of excised iris sphincter of cats and oxen is increased by direct stimulation of the muscle, for it is but slightly antagonized by atropine (Yonkman, 1931). *Ergonovine* is mydriatic (local application in rabbits, M. E. Davis *et al.*, 1935).

Urinary Bladder.—Ergotoxine causes contraction of excised bladder of rabbits, but counteracts other stimulants, including pilocarpine (Streuli).

Ureter.—Ergotoxine inhibits or reverses epinephrine stimulation, but does not interfere with the parasympathetic stimulants (Macht, 1916).

Bronchioles are scarcely affected (D. E. Jackson, 1914).

The **central nervous system** is affected both directly and indirectly, and the effects are correspondingly variable. With moderate doses, the flow through the cerebral vessels is increased. Small doses may cause medullary stimulation (vagus slowing; increased respiration, convulsions, and the like). Large doses of ergot cause *death* by medullary paralysis. It has a narcotic effect for roosters. The *respiratory center* is momentarily depressed by intravenous injection of ergotamine (1 mg. per Kg.) in dogs; but it tends to remove the apnea of epinephrine and nicotine (Bouckaerts and Czarnecki, 1927). The *temperature* is raised in rabbits by 3° to 4.5° C., through the intravenous injection of *ergotoxine*, 0.5 to 1.5 mg. per Kg. This is accompanied by convulsions, but as some rise occurs even after curare, it is not entirely muscular. There is no rise in decapitated animals. The action must be central and probably involves both increased heat production and diminished heat loss. Cats also respond by a rise of temperature; rats, mice and pigs by a fall (Githens, 1917); dogs show practically no effect (Youmans and Trimble, 1936). *Ergotamine* produces hyperthermia and convulsions in rabbits, but requires about double the dosage (Rothlin, 1932). Discordant results with ergotamine were reported for rabbits by von Euler, 1929 (lowering of temperature by diminished heat production), and by Bouckaert and Heymans, 1929 (no effect on temperature or heat production).

The **basal metabolic rate** is increased in rabbits by the convulsant tendency of *ergotamine;* but Bouckaert and Noyons, 1926, claimed marked decrease clinically, by hypodermic injection, and amelioration of the symptoms of *hyperthyroidism*, including the tachycardia, exophthalmos and tremor. *Ergonovine* increases the metabolic rate in rats (Davis *et al.*, 1936). The **blood sugar level** does not appear to be affected directly by ergotamine and ergotoxine; the effects that have been reported were probably indirect results of excitement and other actions. Farrar and Duff, 1928, described hyperglycemia in unanesthetized dogs; but this does not occur if the dogs have been properly trained; nor does it counteract epinephrine glycosuria (Youmans and Trimble, 1930). Rothlin, 1930, stated that ergotamine suppresses epinephrine hyperglycemia in rabbits. It has been claimed that ergotoxine (as also atropine) inhibits phlorhizin glycosuria (Goldberg, 1928).

Urine Output.—Arima, 1934, claimed that ergotamine always decreases the urine volume and the output of salts.

Pruritus.—Ergotamine is reported to give relief, sometimes complete and sometimes permanent, of the itching of jaundice and uremia (Brack, 1930; Snell and Keyes, 1933). It is administered by mouth, 1 mg. in the evening. If this is not effective, it need not be continued. If it is successful, three doses may be taken on each of the two following days (Lichtman, 1936). In herpes zoster, A. Stöckly, 1942, advises 0.5 to 1 mg. hypodermically for six successive days.

Acute ergot poisoning is rare in man, but may occur by attempts at abortion. The symptoms are vomiting, diarrhea, vertigo and confusion, precordial distress, dyspnea, muscular pains, paresthesias and anesthesias, disturbances of vision and speech, epileptoid convulsions, small pulse, loss of consciousness. In pregnancy, uterine hemorrhage and abortion of the dead fetus are frequent. Recovery after severe poisoning may require several days. Rosenbloom and Schildecker, 1914, isolated ergotinine crystals from a patient dead of acute ergot poisoning.

Chronic Ergot Poisoning, "Ergotism."—Epidemic ergotism is mainly of historic interest, but gangrene occurs occasionally from therapeutic administration. The initial symptoms are fairly uniform, but in epidemics they develop into two distinct types, the gangrenous and convulsive, which were long classed as separate diseases. Toward the end the symptoms converge. In a third type, urticaria is the dominant symptom (review, G. Barger, 1938). While ergot is chiefly responsible for the toxic phenomena, these may be complicated by vitamin A deficiency (E. Mellanby, 1930) and by toxic constituents of spoiled grain (Stockman, 1934).

Historical.—Endemic ergotism was formerly common The connection with ergot-contaminated flour was discovered by peasants and reported by Brumer in 1695. Since the cause was recognized these epidemics have been less frequent. The last large epidemic in the United States was in New York in 1825. An extensive epidemic occurred in Russia in 1926 to 1927; a mild epidemic in Manchester, England, in 1928. A comprehensive discussion of the history of ergot is given by Kobert, 1889.

The initial *clinical symptoms of ergotism* are nausea and vomiting, headache, itching, feeling of numbness, formication and other disturbances of cutaneous sensation. The skin may be hyperesthetic to some stimuli and anesthetic to others. These sensory changes *begin at the extremities and spread upward.* This distribution favors the view that they are manifestations of changes in the circulation, since these would make themselves felt first in the extremities.

The disturbance in sensations also involves the *alimentary canal,* as *voracious hunger or loss of appetite.* Digestion is much impaired by the disturbed circulation. Diarrhea and vomiting are common. There are violent and persistent *headache* and central disturbances of the *special senses.* The *motor system* begins to show abnormal symptoms, such as *twitchings* and tremors, most marked in the extremities and in the tongue.

The sensory symptoms persist, but do not become worse. The motor phenomena, the twitchings pass into *spasms,* and then into permanent and often painful *contractures,* beginning with the flexor muscles, the fingers and feet being crooked inwards. The contractures may then ascend to the other joints. The facial muscles participate. The type of these contractures shows that their origin is central. They are not absolutely persistent, but come on suddenly, last for about half an hour, then pass off for a time and reappear. There may be involuntary evacuation of the urine, *tenesmus,* and so forth. The *pulse* is hard and small, pointing to a high blood pressure. Its frequency is variable. It is usually slow, probably largely because of the high pressure.

The symptoms of the initial stage are common to the different forms of ergotism; they can be accounted for partly by the changes in the circulation and partly by the direct action of the ergot principles themselves. In the *second stage* the circulatory disturbances become more marked. The disturbances of sensation and the contractures persist; but to these are added the further phenomena of either the spasmodic or the gangrenous form. Different epidemics run to one type or the other, rarely both.

In the *spasmodic form* the contractures pass into *tonic and clonic convulsions* or *epileptiform spasms,* which may last for many weeks, and then be followed by paralysis. There may be degeneration of the posterior columns of the spinal cord, with tabetic symptoms. Psychoses may be present. The anatomical degenerations make the prognosis unfavorable.

The *gangrenous form* may begin with the appearance of pustules. The limbs swell, most frequently the feet, with a feeling of intense heat ("Saint Anthony's fire"), and intense pain, then numbness and "frost-bite" gangrene. The entire member may be involved in the gangrene. The finger, toe or limb may slough away without bleeding.

The form appears to depend largely on the amount of ergot: if this constitutes less than 10 per cent of the bread, the convulsive type predominates; the gangrenous is more common with 30 to 50 per cent. An ergot content of 1 per cent renders flour poisonous; 7 per cent may become fatal.

The *treatment* of ergot poisoning is symptomatic.

Chronic ergotism in animals takes the course of gangrene; with loss of the comb or wings in birds; of the extremities or tail in mammals. Diarrhea, somnolence and paralysis develop concurrently, but not convulsions (Langecker, 1932).

Somewhat inconclusive animal experiments of E. Mellanby, 1931, indicate that vitamin A deficiency increases the severity of the convulsive form. R. Stockman, 1934, produced phenomena resembling convulsive ergotism by feeding monkeys with rye uncontaminated with ergot. Ratschow and Klostermann, 1938, claimed that ergotamine gangrene of rat tail may be prevented by injection of estrogen in females, of testosterone in males.

O. G. Fitzhugh *et al.*, 1944, found the growth of rats retarded when the food over long periods contained 1 to 5 per cent of ergot. There was no gangrene or vascular lesions, but a high percentage developed neurofibromas of the ears.

Related Fungi.—*Claviceps paspali,* growing on a Southern forage grass, Paspalum, produces toxic effects on feeding. They have not been studied in detail (H. B. Brown, 1916).

Ustilago Maydis.—*Corn Smut.*—A fungus analogous to ergot, found on the maize plant, has been employed by the Negroes for abortion, and stockraisers have also observed that it has an ecbolic effect. Bogdanovic, 1934, injecting fresh extracts into rabbits, reported effects resembling those of ergotoxine and antagonistic to epinephrine, but including hyperglycemia, prolonged fall of blood pressure and intestinal inhibition. W. H. Hunt and Thompson, 1938, found that it causes contraction of excised uterus and produces abortion in cats and cyanosis of cock's comb, but it is much weaker than ergot. Its toxicity is also low. It lowers blood pressure, but does not inhibit the pressor response to epinephrine. Perfusion through the frog leg causes constriction. The activity is not due to an alkaloid or acetylcholine or histamine, but resides in an oily fraction.

Deterioration of Ergot.—The ergot alkaloids and amines are rather unstable substances, and ergot loses its activity with age. Ergotism is said to have occurred only during the first four months after harvest (Poulsson). Many pharmacopeias therefore direct that ergot must not be older than one year. The fluidextracts on which the reputation of ergot is mainly based have probably all been aged for a year before being sold (Eldred, 1913). They are said to deteriorate chiefly within the first six months after their manufacture, then very slowly (Assoc. Amer. Drug Manufacturers, 1923). They should not be sold until past the period of rapid decline. This aging destroys chiefly the amines (M. R. Thompson, 1929), and these are not therapeutically important. The uncertain activity of ergot makes it advisable to employ only such preparations as have been assayed, although the assay methods are not very accurate.

Assay of Ergot.—The U.S.P. requires the bio-assay of ergot by the *cock's comb method* in comparison with ergotoxine ethane sulfonate. This depends upon the production of cyanosis under prescribed conditions. It reflects the therapeutic activity better than any other method. It covers all the therapeutically active ergot alkaloids, and excludes histamine and the other amines. Its accuracy, however, is not great.

The *cock's comb* test was described by Lorinser, 1824; used experimentally by Grünfeld, 1892 and 1895, under Kobert; and applied commercially by Houghton, 1898. The details are prescribed in the U.S.P. H. H. Crosbie, 1934, reported how the accuracy may be improved by color photography. *A chemical color reaction*, based on Van Urk's reaction with para dimethyl aminobenzaldehyde (M. I. Smith, 1930), is given by all the ergot alkaloids, including those that are inactive, and therefore does not always parallel the therapeutic activity (Lozinski *et al.*, 1931). The *method of Broom and Clark*, 1923, utilizes the *epinephrine-reversal* on blood pressure or rabbit's uterus. This is a more accurate measure of ergotoxine and ergotamine, but it does not include ergonovine and is therefore unsatisfactory. *Direct measurement of the effects on the uterus* of guinea pigs and cats is not reliable since it includes the histamine.

Preparations.—*Ergot* (Ergota, Secale Cornutum) is a fungous growth, Claviceps purpurea, from rye. Generally collected in Russia or Spain. Should not be older than one year. (The name comes from the French "ergot," a cock's spur, which it resembles in appearance.)

***Ergot Fluidextract** is prepared from defatted ergot with acidulated dilute alcohol. The potency, by bio-assay, should be equivalent to at least 0.5 mg. of ergotoxine ethanesulfontea per cubic centimeter. Dose, 2 cc., 30 minims. The *Liquid Extract,* B.P., is an aqueous solution preserved with alc.

***Ergotamine Tartrate,** U.S.P. (*Gynergen*), is soluble in water, 1:500. Dose, 0.25 to 0.5 mg. hypodermically, 1 to 2 mg. by mouth. *Ergotamine Tartrate Tablets,* U.S.P.; usual sizes, 0.5 and 1 mg. *Gynergen Solution,* in ampuls, 0.5 mg. in 1 cc. *Ergotoxine ethanesulfonate* is sol. in alc., but slightly sol. in water. Must be stored in an atmosphere of nitrogen, in sealed tubes, protected from light. Solutions deteriorate easily. Dose (subcutaneous or intramuscular injection), 0.5 to 1 mg., $\frac{1}{120}$ to $\frac{1}{60}$ grain.

Ergonovine maleate, U.S.P. (*Ergotrate*); soluble in water (1:36). Dose, by vein or intramuscularly, 0.2 mg.; by mouth, 0.5 mg. *Injection,* U.S.P., a watery solution, usually available as 0.2 and 0.5 mg. in 1 cc. *Tablets,* U.S.P., usually available as 0.2 and 0.5 mg.

Ergotine has been applied to different preparations. Those that occur most extensively in the older literature are: *Ergotine Bonjean:* Aqueous solid extract, purified with alcohol. *Ergotine Wernich:* Dialyzed extract, marketed both as a liquid and as a soft extract. *Ergotine Wiggers:* Dried, alcoholic, purified solid extract.

Haskell, 1914, found that "ergotine" and powdered extract produce the typical effects of ergot, but that the effects on the uterus are weakened much more than those on blood pressure.

OXYTOCICS OF MINOR IMPORTANCE

Gossypii Radicis Cortex, Cotton Root Bark.—The dried root bark of Gossypium herbaceum and other species. This was used as abortifacient by the Negroes of the South and also in Africa (G. W. Harley, 1941). It contains resins, but no alkaloids or tannin (Power and Browning, 1914; Zellner, 1910). Clinical and experimental reports are not favorable; the perfused uterus, however, is stimulated (Scott, 1911).

Peony Root.—Holste, 1916, claimed that this contains an alkaloid that stimulates uterine contractions, constricts blood vessels and increases blood coagulation. This needs confirmation.

"Shepherd's Purse."—Extracts of Capsella *bursa-pastoris* obtained a brief popularity as ergot substitute (H. Boruttau, 1920), but promptly relapsed into oblivion. C. Braga described quite complex pharmacologic effects, including relaxation of the nonpregnant uterus and stimulation of the pregnant. Butturini and Marangoni, 1934, found no ecbolic action, but reported effects on cock's comb similar to those of ergot, cyanosis of the tail of rats and transitory depression of blood pressure without epinephrine reversal.

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UTERINE SEDATIVES AND HEMOSTATICS

A number of drugs with ill defined actions are popularly credited with "quieting the excitability of the uterus," especially the pains of premature labor; with contracting the os uteri; arresting uterine hemorrhage; regulating dysmenorrhea, particularly at puberty and the climacteric; and even with correcting uterine malpositions. It is difficult to conceive a mechanism by which a drug could produce all these actions, except in the imagination. Many of these complaints are so uncertain in their course, and indeed so largely nervous, that it is easy to imagine any results that are desired.

These remedies were mostly taken from uncritical folk medicine and promulgated during the most uncritical period of therapeutics. They owe their continuance mainly to their extensive use in proprietary *"female weakness" remedies.* These in turn rely for their sale on the liberal use of alcohol and exaggerated suggestive advertising. There is practically no serious evidence of the clinical usefulness of these drugs. Excepting hydrastis and cotarnine, which belong to a somewhat different class, there is no record of any competent clinical investigation by experienced critical observers under hospital conditions. The clinical cases published are generally superficially recorded; they usually show evidence of prejudice and exaggeration, and are often vitiated by the simultaneous use of other measures of more evident value. Pharmacologically, most of the drugs of this class are practically inert, especially as concerns the uterus. Since the excised uterus reacts essentially like the uterus *in vivo,* it may be fairly taken as an index of uterine activity. Pilcher, 1916, investigated in this way the drugs used most commonly in these female remedies, employing the relatively high concentrations of 1:1000 to 1:500. He obtained no definite effects with: *Chamaelirium* luteum (*Helonias* diocia); *Leonurus* cardiaca; *Passiflora* dentata; *Mitchella* repens; *Chestnut* bark. The following gave more or less pronounced effects (but not sufficient to confirm any therapeutic value). *Slight Depression: Valerian; Dioscorea* villosa; *Aletris* farinosa; *Ichthyomethia* piscipula; *Pulsatilla* pratensis; *Cypripedium* pubescens; *Scutellaria* laterifolio; *Scrophularia* marylandica; *Senecio* aureus; *Viburnum* opulus. *Inconstant Stimulation: Acer* spicatum; *Cnicus* benedictus; *Viburnum* prunifolium. *Constant Marked Increase of Tone: Caulophyllum* thalictroides. These results were obtained chiefly on the excised uterus of guinea pigs. The excised human uterus required higher concentrations, but gave the same reactions (Pilcher, 1917). None of the above drugs produced any effect in anything like normal doses on the uterus of living animals (Pilcher and Mauer, 1918).

Excised intestines are affected similarly to the uterus. Caulophyllum, however, lowers the amplitude with little effect on the tone. Valerian (oil) depresses the contractions. Viburnum opulus and prunifolium are inactive (Delzell, Burman and Pilcher, 1916).

VIBURNUMS

Viburnum prunifolium and Viburnum opulus have the widest reputation among these uterine sedatives, but their usefulness is no more demonstrated. Illustrative of this is the fact that the drug sold as Viburnum opulus has, for the last twenty years, consisted of the bark of a maple, Acer spicatum (Farwell, 1913, and others). Viburnum prunifolium, or Black Haw, a rather common shrub, was used somewhat in domestic medicine (Lloyd). It was introduced into medical practice mainly by the clinical papers of Phares, 1866, and Jenks, 1876. Both praised it with extravagant enthusiasm. The next ten years were the high tide of its popularity, as judged by an output of seventy-five articles on the subject. The interest then abated equally suddenly, for the next thirty years produced only some fifteen papers. The whole early literature is typical of the loosest class of clinical "evidence." The mechanism of its reputed action is at most a matter of speculation. The only attempts at investigation date from R. L. Payne, 1888, and Sherman, 1896, and these did not include the uterus. They showed that large doses may produce depression of the whole nervous system, without practical significance. La Torre, 1912, interpreted the histologic picture as contraction of the uterus, compressing the uterine vessels. The first real search for uterine actions was made by Lieb, 1914. He believed that he observed stimulation of the excised uterus. More extensive investigations by Pilcher, 1916; by A. P. Matthews and Hager; by Hager and Becht, 1919, and by Hale, gave generally negative results under all conditions (uterus pregnant and nonpregnant; *in situ* or excised). W. E. Evans *et al.,* 1942, claimed to have isolated a uterine depressant substance from V. prunifolium. Neither viburnum has any effect on excised intestine.

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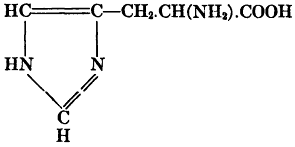
HISTAMINE

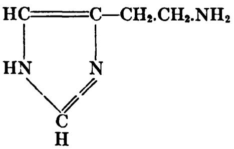
Histamine (*beta-iminazolyl-ethylamine; ergamine, ergotidine*) is partly responsible for the actions of aqueous extracts or ergots. It occurs also, mostly in combined form, in all tissues, and is liberated in putrefaction. It is destroyed in the digestive tract and has little effect when administered by mouth; but when injected subcutaneously or intravenously, it produces intense direct stimulation of the tonus or rhythm of smooth muscle, similarly to pituitary extract; and lowers blood pressure, by dilating the capillaries, similarly to peptone or anaphylactic shock. There is considerable difference in the susceptibility of the various autonomic organs, and this has no relation to their nerve supply. In organs inhibited by epinephrine, the latter is a more powerful antagonist to histamine than is atropine. Histamine is used clinically to test the secretory capacity of the stomach, and for the relief of pain in neuritis, chronic rheumatic affections, myositis and secondary myalgia.

Susceptibility of Different Muscles and Glands.—The stimulation of smooth muscle is most marked in the uterus; the bronchioles are also highly sensitive; the intestine, arteries and spleen are less susceptible; the bladder and iris do not respond (Quagliariello, 1914). Cardiac muscle is mildly stimulated; skeletal muscle is not affected. There is a weak pilocarpine action on glands (Dale and Laidlaw, 1910).

Chemical Structure.—Histamine is derived from histidine by the loss of a carboxyl group:



= Histidine



= Histamine

Occurrence in Tissues.—Histamine occurs in extracts of all tissues, animal and vegetable. Some is perhaps free, but the greater part is liberated by protein cleavage, effected by acids, by ferments or by bacteria. Kidney and liver tissue and their extracts form histamine by enzymic decarboxylation of histidine, kidney being four or five times more potent than liver. It can also be formed by nonenzymatic processes (P. Holtz *et al.*, 1938; E. Werle and Hermann, 1937).

Small amounts of histamine may be estimated by *biological tests* (rectal cecum of fowl, Barsoum and Gaddum, 1935; atropinized guinea pig intestine, C. F. Code, 1937).

From biological tests, Anrep, Barsoum *et al.* (1939) concluded that histamine is normally present in the *blood*, its concentration being especially high in rabbits and low in cats, and 10 to 60 times higher in the corpuscles than in the plasma. In clotting, a considerable amount passes from the corpuscles to the serum (C. F. Code, 1937). The *organ content* is not materially different in rats, guinea pigs and other species (J. Martin and Valenta, 1939).

Formation of Histamine in Muscle.—Burns and a considerable variety of chemical and physical agents cause release of histamine from tissues (H. Bachmann, 1938). The concentration of histamine in the venous blood of skeletal muscles rises when they are exercised, but not when they are resting (Anrep, Barsoum *et al.*, 1939). The heart muscle liberates it continuously, but also proportional to its work (Anrep, Barsoum and Talaat, 1936). Histamine is released in the active contraction of the smooth muscle, induced by acetylcholine, potassium chloride or pituitary extract (Ambache and Barsoum, 1939).

The disappearance of injected histamine from the blood stream occurs rapidly, the greater part within fifteen minutes in rats. The highest concentration is then found in the kidneys, but most has been destroyed. After excision of the adrenal glands, it disappears more slowly from the blood and tissues (B. Rose and Browne, 1938). It leaves the blood less rapidly in dogs (C. A. Dragstedt and Mead, 1935).

Destruction in Perfused Organs.—With Starling heart-lung preparations, histamine was destroyed by all organs that have been studied, most actively by the kidneys, then the liver, then heart, lungs, hind limbs and intestines (Steggerda, Essex and Mann, 1935). Very large oral doses are therefore tolerated without toxic effects (300 mg. by guinea pigs, 225 mg. by man), although 1 mg. by vein produces alarming symptoms in man. The protection is not due to the liver, but to rapid *destruction of histamine in the intestines* (Koessler and Hanke, 1924). This precludes intoxication from any histamine that might be formed by bacterial putrefaction of proteins. None has been isolated from the intestinal contents (H. Burchard, 1934).

Circulation.—In most species of animals the injection of histamine produces an extensive fall of blood pressure, which may be short or lasting, according to the dose. With large doses it is persistent, and presents the essential phenomena of "traumatic shock" (Mellanby). The fall is due to dilatation and increased permeability of the capillaries, analogous to inflammation, with slowing of the circulation by stagnation of the blood. Similar effects occur in peptone, anaphylactic and traumatic shock, and these may be due in part to the formation of substances with histamine actions (Dale and Richards, 1918).

Late Lesions.—Death from severe and prolonged histamine shock occurs usually by cardiac failure. Dogs that survive generally develop degenerative lesions in the aorta, especially the media, and in smaller arteries; also myocardial degeneration, prepyloric gastric ulcers, pericentral hepatic necrosis and focal splenic fibroblastic proliferation (Hueper and Ichniowski, 1944).

Muscular Vasodilator Substance.—Anrep and his associates, 1935 and 1936, claimed that histamine is the dilator substance found in the venous blood coming from contracting skeletal muscle and from the heart, which is responsible for the increased local blood supply during muscular exercise.

The *vasomotor center* is not affected directly, but the fall of blood pressure and the respiratory disturbances usually produce moderate stimulation (Pilcher and Sollmann, 1915).

Denervation.—Dale and Richards, 1918, confirmed that the depressive responses to histamine as well as to epinephrine and acetylcholine are peripheral and are, indeed, generally increased when the nerve supply has completely degenerated.

Susceptibility of Different Animals.—Man, dog, cat, monkey and fowl respond by fall of pressure; rabbits and guinea pigs show a rise (Dale and Laidlaw, 1911). The acute toxicity varies considerably with the conditions (Dale and Laidlaw, 1920). *Rats* are highly resistant to the histamine actions, although the histamine content of their organs does not materially differ from those of the very susceptible guinea pigs and rabbits (J. Martin and Valenta, 1939). Their resistance is lowered by changes of the electrolyte balance analogous to those induced by excision of the adrenal glands (Perla and Sandberg, 1939; Crivellari, 1927), and is restored by administering desoxycorticosterone (B. Rose, 1939). Excision of the thyroid gland is reported to render guinea pigs resistant to histamine and to anaphylaxis. The puerperal state and nursing also increase the resistance to histamine shock (Spinelli, 1929). *Graduated injections of histamine* for two or three weeks raise the tolerance of guinea pigs to five or six times the normal, and furnish considerable protection to anaphylactic shock from horse serum (E. A. Smith, 1939); similarly with *oral administration* (L. Farmer, 1939).

Clinical Symptoms.—Intravenous injection of 0.5 to 1 mg. of histamine into healthy young men causes momentary flushing of the face, succeeded by pallor; metallic taste, dizziness, faintness, frontal headache and rapid pulse, sometimes weak. The headache lasts several hours, the other effects less than half an hour. There is a moderate leukocytosis for three to five hours. Hypodermically, 2 mg. produce the same effects in less degree (Moon *et al.*, 1935).

The *headache* has been attributed to dilatation of the large arteries of the brain (G. A. Schumacher *et al.*, 1940). Migraine headache, which is explained by the same mechanism, is hypersusceptible to histamine (von Storch, 1940).

Clinical Effects on Circulation.—Intravenous injection of 0.001 mg. of histamine per Kg. of body weight causes prompt dilatation of the minute vessels of the face and brain. The time required for this may be used as index of the *blood flow velocity* (S. Weiss *et al.*, 1939). *Continuous intravenous* injection in man at constant rate maintains uniform effects for a considerable time, so that the histamine must be inactivated as fast as injected. A concentration of 1:20,000,000,000 of circulating blood gives recognizable effects. With the standard dose, the heart rate is quickened, without change of blood pressure, but with dilatation of the brain vessels and less dilatation of the skin vessels (Weiss, Ellis and Robb). With 2.75 mg. of the diphosphate in 250 cc. of saline, the A-V conduction time is shortened and the amplitude of the T wave is diminished, roughly proportional to the rate of injection. The changes are insignificant and do no permanent functional damage to the myocardium (G. A. Peters and Horton, 1944).

Heart.—Large doses of histamine injected intravenously or into the heart of dogs, cats, rabbits or guinea pigs dilate the right heart, probably through increased resistance in the lung vessels. Repeated hypodermic injections result in hypertrophy of the right heart. Morphologic changes in the heart tissue are produced both by acute and repeated injections (E. Kirch, 1933).

The *perfused mammalian heart* shows a short and slight slowing, followed by considerable quickening with increased excursions. The isolated *frog heart* is slowed (Eims, 1913) in winter, stimulated in spring (Lissak and Kokas, 1938).

Capillaries.—Observing these with the microscope in the living animals, by Lombard's method, Hooker, 1920, noted that the injection of histamine into cats produces prompt dilatation, sometimes preceded by brief constriction. The effects are not influenced by section of the nerves and are therefore peripheral. Dilatation of the capillaries and small arterioles and venules has also been observed in the omentum of the cat (A. R. Rich, 1921), in the mesentery of mice (J. Wolff, 1923) and in the human skin (Carrier, 1922). The production of skin edema is discussed below. The capillaries of frogs are not dilated (Krogh).

Perfused organs respond by vasoconstriction if the histamine is perfused in saline; but in the presence of blood and epinephrine, histamine dilates, and therefore reproduces the depressor effect of intact animals (Dale and Richards, 1918). The *coronary vessels* are dilated in dogs (L. N. Katz and Lindner, 1939).

Excised arteries are constricted by histamine, in all species and in nearly all situations (Dale and Laidlaw, 1911), including the coronary (Barbour, 1913) and the pulmonary arteries (Anderes and Cloetta, 1916), but not the liver veins (Berezin, 1914).

Pulmonary vessels are constricted in lung sections (Gilbert, 1938), lung perfusion (S. Okada, 1940), and apparently in intact animals, for the pressure in the pulmonary artery rises and the volume of the lung diminishes, even when the pressure in the systemic arteries is unchanged (Anderes, 1915). Woodbury and Hamilton, 1941, attributed the rise of pulmonary arterial blood pressure in cats and rabbits to pulmonary vasoconstriction, but in dogs to increased output of the right heart. Berezin, 1914, stated that the constrictor effect in the excised vessels is removed by atropine, and the like.

Abe, 1920, and Dale attribute the fall of blood pressure by histamine, peptone, serum, to interference with the pulmonary circulation, partly by bronchial spasm and partly by direct contraction of the pulmonary vessels.

Clinical Effects on Cerebral Vessels and Cerebrospinal Fluid Pressure.—Intravenous injection of histamine without anesthesia or with amytal anesthesia dilates the cerebral vessels and raises the cerebrospinal fluid pressure. Under ether, the cerebral vessels are already dilated and histamine does not dilate them further; indeed, the fall of blood pressure may narrow them and lower the cerebrospinal fluid pressure (H. S. Forbes *et al.*, 1929). Similar effects occur in dogs, with small doses (Weinberg, 1933). If a bronchial spasm occurs, this raises the cerebrospinal fluid pressure through asphyxia (Dixon and Halliburton, 1914).

Theory of Deficient Blood Return.—Mautner and Pick, 1915, suggested that the fall of pressure after histamine, peptone, and so forth, could be explained by obstruction to the return of the blood to the heart; for instance, by spasmodic constriction of the intestinal arterioles, and of the lung vessels; or by choking of the liver capillaries (K. Gollwitzer-Meyer, 1932). There is, in fact, congestion of the liver and of the splanchnic vessels in peptone shock or anaphylaxis, but not, according to Dale and Richards, in the evanescent histamine fall. It is therefore more probably a secondary result. Portal obstruction is not the essential factor in the histamine fall, for it occurs in eviscerated animals. The latent period of the fall is also suggestive. It is shortest when the injection is made into an artery, longer with a vein, and longest with the portal vein. This indicates that the action is on a structure between the arteries and veins, that is, on the capillaries. Gantner and Schretzenmayr, 1930, concluded that the vascular dilatation in the extremities, kidneys and splanchnic area suffices to explain the fall of blood pressure without invoking blockade of the liver or lung. The increase of thoracic lymph flow, which comes chiefly from the liver, has been attributed to constriction of the hepatic veins, with consequent rise of pressure in the capillaries of the liver (Yamasaki, 1939).

The *urine flow* is decreased (in dogs) by hypodermic or intravenous injection of histamine, chiefly by the fall of blood pressure, together with the increased excretion of water into the alimentary tract, by the gastric juice, saliva and pancreatic juice. Stasis of the blood into the liver may contribute to the oliguria (Molitor and Pick, 1923). In *perfused kidney*, the smallest effective concentrations of histamine cause constriction, while similar concentrations increase the perfusion flow through the extremities and intestines (Morimoto, 1928).

The *plasma volume* is not materially changed by histamine injection, notwithstanding the rapid fall of blood pressure, in contrast to traumatic shock. Indeed, there is generally some increase, by mobilization of the blood from the spleen and other depots (I. J. Deyrup, 1944; Brednow, 1931).

The coagulability of the blood is not altered, in contrast to peptone (Dale and Laidlaw, 1911; Loewit, 1913).

Leukocytosis.—Hypodermic or intravenous administration of histamine causes moderate increase of the polymorphous neutrophils, sometimes preceded by transient leukopenia. In man, with 0.5 to 1 mg. by vein, the increase averages about 3000 and lasts for three to five hours (Moon *et al.*, 1935). Histamine causes abundant *emigration of leukocytes* from blood vessels, but is not chemotactic (review, McCutcheon, 1946).

Histamine Urticaria.—The application of a drop of histamine, 1:1000, to the scarified skin produces brief pallor, followed by reddening and the formation of a temporary urticarial wheal (Eppinger, 1913). The hypodermic injection of 0.5 to 1 mg. of histamine may be followed by erythema over the entire skin. Thomas Lewis, 1927, divides the response to intradermic injection of histamine into four phases: (1) an immediate "*white reaction,*" a local paling due to the mechanical expression of blood from the minute vessels by the tension of the injection; (2) in about twenty seconds, a "red reaction," a small red spot immediately about the puncture, due to dilatation of the capillaries and venules, occurring also in denervated skin; (3) shortly after this a spreading "red flare," attributed to arteriolar dilatation and active hyperemia by a local nervous reflex; (4) in one or two minutes, a small wheal, a localized edema, due to increased permeability of the capillary endothelium. Similar reactions, but of various degrees, occur in dermatographia, and by the application of a variety of substances, for instance, peptone, morphine and its derivatives, to a small degree by atropine, cocaine, formaldehyde, calcium and a number of amino compounds; in susceptible individuals also by quinine and the like, and by certain proteins and anaphylactic poisons (Sollmann and Pilcher, 1917). No definite relation of the urticaria to other actions or to chemcal constitution has been recognized. The urticaria is a particular, limited type of dermatitis, consisting in congestion by direct dilatation of the local capillaries, reflex dilatation of the neighboring arterioles and increased permeability of the capillaries, leading to local edema. Dogs and goats also respond by wheals to intradermal injection of histamine; cats, rabbits and guinea pigs do not (M. L. Darsie, Perry *et al.*, 1945). Identical phenomena occur in other irritations of the skin, for instance mechanical or thermal burns. Th. Lewis and Grant, 1924, suggested that these are due to the liberation of the histamine-like substance. Menkin, 1936, found that all inflammatory exudates increase the permeability of the skin capillaries, but that this is not due to histamine or a closely related substance, for their effect on intestinal motility is the reverse of that of histamine. The subject of capillary pressure and permeability is *reviewed* by E. M. Landis, 1934.

Diagnostic Applications of Histamine Wheals.—These bring out the yellow color of the skin in *latent icterus* (O. Klein, 1931). The urticarial response is diminished if the arterial blood supply is decreased, as in arteriosclerosis or Buerger's disease (Haxthausen, 1938). It is also a test of peripheral nerve function, since the "flash" hyperemia does not occur where the sensory nerve fibers have degenerated (L. H. Loeser, 1938). The susceptibility of the *bronchial musculature* to histamine does not go parallel to its edemic action on the skin (Samter, 1933), and this is therefore not an index of allergic tendencies.

Role of Histamine in Anaphylactic Shock.—The occurrence of histamine in pituitary extract, peptones, secretin and other organ extracts, and especially those prepared with acid and heat, and the striking resemblance of their effects to those of histamine, suggested that histamine is responsible for their actions (Abel and Kubota, 1919; bibliography). Histamine is released by perfusion of the antigen through the lungs of sensitized guinea pigs (H. Schildt, 1936), and from the red blood cells of sensitized animals when they are treated with antigen *in vitro*, in quantity sufficient to have marked effects (G. Katz, 1940). In guinea pigs, the plasma concentration of histamine rises in *anaphylactic shock* to two to thirteen times and in dogs even to more than eighty times the normal level coincident with the fall of blood pressure (C. A. Dragstedt and Mead, 1936; C. F. Code, 1939); but rabbits, horses and calves do not show a significant increase (B. Rose and Weil, 1939; Code and Hester, 1939). With rabbits, the histamine content of the whole blood falls rapidly in anaphylactic shock; the tissue concentration is not changed (B. Rose, 1940). The blood histamine also falls in marked types of clinical shock and in agonal states (B. Rose and Browne, 1940). Shock by rattlesnake venom and crystalline trypsin injection into guinea pigs increases the histamine content of the blood. Snake venom, staphylococcus toxin and peptone liberate histamine when perfused through the lungs of guinea pigs or cats (Feldberg *et al.*, 1937).

Traumatic shock (produced by contusion of the leg or extruded intestines) is not accompanied by histamine increase (Dragstedt and Mead, 1937). Blood drawn from the traumatized leg does not produce shock when injected into a normal animal (Parsons and Phemister, 1930; J. R. Bell, Clark and Cuthbertson, 1938), contradicting the toxemic theory of shock proposed by Dale, Laidlaw and Richards, 1919. Histamine leads to irrecoverable low blood pressure only if other factors are superimposed (H. Rein, 1937). The clinical phenomena of shock depend on inadequate blood supply of the tissues, due to diminished blood volume, and this due chiefly to hemorrhage and to exudation of the plasma fluid into the injured tissues (reviews, A. Blalock, 1936, C. J. Wiggers, 1942).

Salivary Secretion.—In *anesthetized dogs*, 1 to 7 mg. of histamine intravenously increases the salivary output, partly by a muscular action, pressing out the contents of the alveoli and ducts, and partly by increasing the secretion. Atropine abolishes the latter effect in the submaxillary, but not in the parotid, gland. The submaxillary responds to much smaller doses of histamine. The submaxillary saliva secreted in response to histamine has a higher organic content and a lower ash than that of chorda tympani stimulation. Previous injection of histamine diminishes the response to pilocarpine and to chorda stimulation (Stavraky, 1931).

With *cats,* intravenous histamine injection usually causes submaxillary salivation, which is antagonized by epinephrine (M. E. MacKay, 1929). The increase appears to be indirect, for it does not occur if histamine is injected into the artery of the gland. This, however, greatly increases the response to chorda tympani stimulation, but not acetylcholine. The chorda potentiation is increased by physostigmine, abolished by atropine (O. S. Gibbs and Clanahan, 1937).

Gastric Secretion.—Histamine is the most potent known excitant of gastric secretion, in doses that have little or no effect on blood pressure. *Gastrin,* the secretory-excitant principle of gastric extracts, is probably histamine or a closely related derivative; *secretin,* the corresponding principle of duodenal extracts, is probably also related; indeed, the intramuscular injection of histamine stimulates pancreatic and salivary as well as gastric secretion (Keeton *et al.*, 1920). The stimulation of gastric secretion involves both the acid and the volume. It is used as a diagnostic test, to differentiate between pseudo-achlorhydria, which responds to histamine, and true achlorhydria, which does not respond.

In normal individuals 0.5 mg. of histamine hydrochloride (= 0.85 mg. of the phosphate) intramuscularly produces maximal secretion of acid in half an hour to an hour, persisting for over one and a half hours. In achylia vera, the acid response is absent; in pseudo-achylia it is present, although it may be more or less decreased. The injection produces rather marked side actions: headache, vertigo, flushed face, large urticarial wheal at the site of the injection. It has therefore been suggested to reduce the dosage to half, which is active in normal individuals; but this may fail in pseudo-achylia (Mathewson, 1935).

Histamine should not be injected into patients with *aortic disease.* Death occurred in such an instance within half an hour after the dose of 0.8 mg. (Maijala, 1938).

In *rats,* gastric secretion is not increased, even by 5.5 mg. of histamine phosphate hypodermically (M. H. F. Friedman, 1943).

Production of Gastric Ulcer by Histamine.—Repeated injection of large doses (7½ mg.) of histamine into rabbits produces acute gastric ulcers such as those of pilocarpine, but with more marked vascular changes and edema. They probably result from trauma by the strong peristalsis, and are therefore less marked in fasting animals. Gastric ulcers are also produced by hypodermic injection of methylamine and other *aliphatic amines* which increase gastric acidity. It is more marked if the liver was previously injured by chloroform or phosphorus (Kanatake, 1938).

Histidine against gastric ulcer was introduced by A. G. Weiss and Aron, 1933, on a theory that deficiency of this amino acid might be concerned in the production and persistence of peptic ulcer. They believed that they had confirmed this on the experimental peptic ulcers in dogs, and several clinicians reported benefits in a large proportion of patients from daily hypodermic injections of histidine hydrochloride (5 cc. of 4 per cent), continued for several weeks, with the patients on ordinary diet. However, carefully controlled comparisons (K. A. Martin, 1936; D. J. Sandweiss, 1936; Flood and Mullins, 1936) show that the results were no better, either in kind or degree, than those obtained in alternate patients with the ordinary alkali and diet treatment; either might succeed when the other had failed. There was no constant or marked effect on the acid secretion. The ulcer itself was not improved. About 40 per cent of the patients showed mild subfebrile reactions, not connected with the improvement. The relief appeared to be purely transient and symptomatic, and could indeed be obtained by injections of distilled water. Histidine has no effect whatever on the secretory functions of Pavlov stomach dogs; nor does it alter the tonus or movement of excised intestines (L. B. Goodman and Bearg, 1938); but in guinea pigs, 10 mg. of histidine produce immediate and complete relaxation of the intestinal contractions provoked by histamine. It also antagonizes the stimulation of excised guinea pig uterus by histamine or pituitrin, and generally smooth muscle stimulation by acetylcholine, physostigmine or barium chloride (B. N. Halpern, 1939).

Histidine in Pregnancy Urine.—This has been demonstrated in 90 per cent of gravid women, but only in the latter months of pregnancy (Voge, 1929; Gertler, 1936). It has been attributed to inhibition of liver histaminase (Kapeller-Adler and Haas, 1935).

Histamine on Intestinal Motility.—With anesthetized dogs and cats, intravenous injection also causes marked stimulation, which is diminished but not abolished by atropine. Hypodermic injection requires more than four times the intravenous dosage, and injection into the intestinal lumen is ineffective with two hundred times the dose (McKay, 1930; Gruber and Robinson, 1929). With excised intestines, the stimulating action is much weaker than for most other smooth muscle; dilute solutions may even inhibit (Planelles, 1924). Calcium salts intensify the stimulation (Vanysek, 1914). The histamine stimulation is antagonized by various anesthetics (L. Farmer, 1938). Its inhibition by histidine, arginine and cysteine, in rather high concentrations, differentiates it from other muscular stimulants (D. Ackermann and Mauer, 1944).

Bronchioles and Respiration.—Intravenous injection of histamine produces violent dyspnea and pulmonary emphysema, similar to anaphylaxis (Baehr and Pick, 1913), by acute obstruction of the bronchioles through spasm of their muscle and congestion and edema of their mucosa (D. E. Jackson, 1914). The pulmonary arteries are also constricted. These effects do not occur in rats. The bronchiolar spasm is antagonized by atropine and epinephrine (Sollmann and Gilbert, 1937), also by cocaine, not by ergotamine (Swanson, 1929), nor by histaminase or nicotinic acid (A. J. Gilbert and Goldman, 1940).

Histamine for Diagnosis of Pulmonary Tuberculosis.—Hypodermic injection of 1 cc. of 1:1000 solution, which causes no respiratory disturbance in normal individuals is reported to produce transient moist rales in three to five minutes in 90 per cent of affected patients (Videla and Lamarque, 1935).

Uterus.—Clinically, hypodermic injection of ⅓ to 2 mg. produces prompt and powerful but brief stimulation of the parturient or postpartum uterus, with spasmodic contraction, beginning in one or two minutes and lasting for half an hour (Bourne and Burn, 1927; Jones and Barlow, 1937). Its use is not advisable, as it causes undesirable side actions: marked vasodilatation, rapid pulse, headache, violent vomiting. *The excised uterus* is also stimulated in the human (Kehrer, 1911; Guggenheim, 1914), pregnant and nonpregnant cats, rabbits and guinea pigs (Barger and Dale, 1910); but the rat uterus is relaxed (Fuehner, 1913; constituting a difference from pituitary extract, Tate, 1921).

Excised ureter is stimulated by dilute, depressed by more concentrated solutions (Gruber, 1928). The *urinary bladder* is not stimulated in living animals (Abelin, 1929).

Iris.—Injection of histamine into the carotid artery dilates the pupil of dogs and cats, but constricts it in rabbits. Injection into the anterior chamber produces the same effects, except in dogs, where the dilatation is followed by constriction (Matsuda, 1929).

Blood Sugar Level.—Hyperglycemia is reported from intravenous injection of small doses of histamine in guinea pigs (La Barre, 1926). Histamine activates *carbonic anhydrase.* This is prevented by low concentrations of zinc (E. R. Main and Locke, 1941).

Concentration Gradient.—Histamine produces its effects only when it is applied suddenly; if it is added slowly (*f. i.*, to the excised uterus), it is inactive. A given concentration soon loses its effect, but raising the concentration again induces contractions. Similarly, rapid intravenous injections are much more toxic than slow injections (E. S. Karady, 1941).

Frequent graduated injections of histamine during two or three weeks increase the tolerance of rabbits (Eichler and Killian, 1931), dogs (H. R. Jacobs and Mason, 1936), cats (Karady, 1938) and guinea pigs. They furnish considerable protection against anaphylactic shock from horse serum (E. A. Smith, 1939); similarly with oral administration (L. Farmer, 1939). In dogs, daily intravenous injections sufficient to produce cardiac acceleration (1.3 to 13 mg.) gave no cumulative change of blood count or chemistry, and no tissue damage (G. H. Ettinger *et al.*, 1936). H. R. Jacobs and Mason, 1936, also found no tissue damage in a dog which had received 2322 mg. of histamine intravenously in the course of sixty days. McCarrison, 1924, had claimed that this retards or inhibits the growth of young animals.

Hair growth of underfed albino rats is stimulated by daily hypodermic injection of 1.5 mg. of histamine, as with local irritant (E. O. Butcher, 1940).

Preparations.—*Histamine Phosphate,* U.S.P., the acid phosphate of β-iminazolylethylamine. Colorless crystals, soluble in water (1:4). Average dose, 0.3 mg. intramuscularly. *Histamine Phosphate Injection,* U.S.P., in water for injection, is available in ampuls, 1 mg. in 1 cc. *Histamine hydrochloride* is hygroscopic and tends to deteriorate, especially when in solution (Nelson, 1923).

Imidazol and other histamine derivatives also stimulate smooth muscle, but are less active than histamine (Auvermann, 1918; Dale and Dudley, 1921).

PARAPHENYLENEDIAMINE

This substance, $C_6H_4(NH_2)_2$, also called *orsin,* is used extensively for dyeing hair and furs brown and black. Its use is dangerous since it may result in violent local dermatitis and sometimes in serious systemic poisoning (Cole, 1924), with histopathologic changes in the central nervous system, especially the midbrain (C. Davison, 1943). Dyeing of the eyelashes has caused serious ophthalmia and permanent blindness (J.A.M.A., 1933, *101:* 1558). The susceptibility varies considerably. Para- and ortho-aminophenol, and diaminophenol, related substances used in hair dyes, also cause dermatitis; likewise orthotoluidinic and pyrogallic acid. Paraphenylenediamine, and its dimethyl and diethyl derivatives and metaphenylenediamine, which have similar actions, are employed to accelerate the vulcanization of rubber, and form a toxic hazard in this industry. They are probably decomposed in the vulcanization, but it is not known whether the products formed are toxic (Hanzlik, 1923).

Clinical Phenomena.—The local effects consist in severe dermatitis. The systemic phenomena sometimes observed after the application of hair dyes include vertigo, gastritis, asthenia, diplopia, lacrimation, chemosis, exophthalmos, asthma, exfoliative dermatitis. Industrial workers suffer chiefly from eczema and asthma.

The **peripheral actions** agree in principle with those of histamine; that is, (1) stimulation of smooth muscle, regardless of its innervation. This includes bronchial constriction, which is partly responsible for the asthma; and (2) increased permeability of the capillaries, resulting in the inflammatory and edematous phenomena.

Other Systemic Effects.—Hypodermic injection of paraphenylenediamine into dogs causes hemolytic anemia, reducing the red blood cells to a half or a fourth in forty-eight hours (J. E. Davis, 1946). All the phenylenediamines produce rise of blood pressure, stimulation of respiration, fall of temperature, tremors, convulsions, coma and death. With large doses the animal may die before the edema can develop. Frogs show a narcotic action.

In all the actions, systemic and edemic, the para *isomer* is the most potent and the ortho the least.

Edema Production.—The oral or subcutaneous administration of paraphenylenediamine (0.2 Gm. per Kg.) to rabbits is followed in about one and one-half hours by an intense watery edema of the entire head (Meissner, 1919). This increases to the next day, and gradually disappears by the sixth day, if the animal survives. Not all rabbits develop the edema. It occurs generally in cats and dogs, but not in rats (Tainter, James and Vandeventer, 1929). It is due to increased permeability of the vessels, and may be prevented by diminishing the local blood supply (Tainter and Hanzlik, 1924).

A. R. Johnston, 1928, however, considers the action of amines to be directly on the tissues, and not on the pressure or capillary permeability. The reason for the restriction of the edema to the head is not known. It is not strictly specific, for the edema involves any other part of the body if it is rubbed with turpentine (Gibbs, 1931). In dogs, a single injection of 30 mg. per Kg. produces edema in various situations. The eyes show signs of irritation. Surviving animals develop acute hemolytic anemia, persisting for five to thirty days (J. E. Emerson, 1946). The meta-isomer does not produce head edema, but instead causes hydrothorax, which does not occur with the para-compound.

Quinone-Diïmine.—On exposure to air paraphenylenediamine in solution is promptly oxidized to this compound, $C_6H_4(NH)_2$, which is presumably the dyeing agent. It is also formed in the respiratory tract if paraphenylenediamine is inhaled. It produces violent irritation in sensitive individuals, but soon oxidizes further to "*Bandrowski's base,*" which is less irritant, and then to still less active products. It has been suggested that it is responsible for the pharmacologic actions of paraphenylenediamine, but the evidence is not conclusive. R. L. Mayer, 1928, attributes the actions of paraphenylenediamine, metol (developer), pellidol and related azo dyes to quinone, $O.C_6H_4.O$, formed by their reduction in aminophenol and subsequent oxidation.

Edema by Other Aromatic Amines.—The hypodermic injection of phenylenediamine, metatoluylene-diamine, acetyl-phenylhydrazine (pyrodine) and toluyl-hydrazine produces effusions into the serous cavities. These are not due to hydremia, the blood being rather thickened. Probably the permeability of the capillaries is increased (L. Hess and Mueller, 1915).

Urticaria.—Many amines produce urticaria when applied to the scarified skin; for instance, phenylethylamine, phenylenediamine, hydroxylamine, and the like (Sollmann, 1917).

Drug Purpuras.—Hemorrhages into the skin have been reported as following a variety of drugs, chiefly acetphenetidine, aniline, antipyrine, arsphenamine, atropine, barbiturates, ergot, iodine compounds, mercurials, pyridine, quinine, salicylates. They are sometimes associated with low blood platelet count, but more often not. Some are definitely allergic, permitting passive transfer. This has been reported for quinine and ergot (Peshkin and Miller, 1934).

Toluylenediamine, $CH_3.C_6H_3.(NH_2)_2$.: Injection of 0.05 to 0.08 Gm. into dogs results in bilirubinemia within ten hours (Hiyeda, 1927). McGowan *et al.*, 1936, attribute this to diminished excretion of bilirubin and bile acids into the bile, so that they accumulate in the blood. M Bodansky, 1938, found further evidence of liver injury by meta toluylenediamine, as increase of blood cholesterol to three times and of phosphatase to a hundred times the normal level. The albumin:globulin ratio was decreased to half.

Ethylenediamine, $NH_2.CH_2.CH_2.NH_2$, has a rather low toxicity; the minimum fatal dose for mice is 0.75 Gm. per Kg. hypodermically. With *rabbits*, nearly fatal doses (0.4 Gm. per Kg. by vein or hypodermic) produce lacrimation, salivation, temporary respiratory stimulation, lowering of the temperature, slight general depression and transient diarrhea. The blood pressure falls (often with 1 mg., hypodermically) by a central action. Smaller doses (0.1 mg. per Kg.) produce only a fall of temperature. Daily injections decrease the susceptibility to this effect (Barbour and Hjort, 1920). With *frogs*, it causes chronic convulsions and narcosis. It has rather feeble amine actions on *excised organs*. Intestines are relaxed with epinephrine; but the responses of the uterus and blood vessels may be the opposite of those to epinephrine. Perfusion of rabbit's ear or frog leg sometimes constricts and sometimes dilates the vessels (Anan, 1927).

Ethylenediamine increases the solubility of the *methyl xanthins* (see Aminophylline). It has been claimed that it aids them by dilating the coronary vessels, but this is probably incorrect. K. H. Osterwald and Meurer, 1939, claim that *diethanolamine*, $HN(CH_2CH_2OH)_2$, has a favorable action on cardiac output and coronary flow. They also investigated isopropanolamine.

Ethylenediamine Solution, U.S.P., contains about 69 per cent in water. It has an ammonia-like odor and a strongly alkaline reaction.

Hydrazine ($NH_2.NH_2.H_2SO_4$).—When injected into dogs, hydrazine sulfate lowers the percentage of sugar in the blood and the hepatic glycogen without any glycosuria. The hepatic cells degenerate, but recover if the injection was not fatal. The hypoglycemia appears to be due to increased sugar combustion, as indicated by the respiratory quotient. Injected dextrose is also oxidized more rapidly. There is no specific influence on heat production (Underhill and Murlin, 1915). The production of anhydremia and anemia by hydrazine, *phenyl hydrazine* (see Index) and other hydrazine derivatives was studied by Bodansky, 1924.

Ethylene imine, C_2H_4NH, when absorbed from the human skin or inhaled as fumes, does not produce immediate discomfort, but subsequently there may be severe vomiting and inflammation and edema of the mouth, throat and eyes (Danehy and Pflaum, 1938).

Trimethylamine, $(CH_3)_3N$, acts as a sex hormone, causing frogs to moult their skin and prepare for mating. Very dilute solutions increase flower production in tomato plants. It stimulates the growth of plant tumors after inoculating the plant with tumor bacteria (Havas, 1938).

Triethanolamine, $N(CH_2.CH_2.OH)_3$, has no deleterious effects when low concentrations are ingested with food. Death in acute poisoning is probably due to the alkalinity. It is absorbed through the skin (Kindsvalter, 1940).

Allyl amines, $CH_2{:}CH.CH_2.NH_2$, when inhaled by mice, produces irritation of the nose and mouth, congestion of the eyes, irregular respiration, cyanosis, excitement, convulsions, coma and death. The skin is not irritated by direct application (E. R. Hart and Leake, 1939).

REACTIONS RESEMBLING THOSE OF HISTAMINE

Phenomena resembling closely those of histamine are produced by the injection of many tissue extracts, by peptones, secretin and other products of partial protein cleavage, by blood serum, bacterial products, snake venoms, extracts of traumatized tissue, citrinine (Ambrose and De Eds, 1946), by the injection of many colloids; and in the course of anaphylaxis and of traumatic shock. In some cases the phenomena may be due to the presence of histamine or a near derivative. In most cases, however, the correspondence of the effects is not complete (Loewit, 1913); in some it is only superficial.

SECRETIN

Pavlov showed that the presence of acid chyme in the duodenum is the normal stimulus to the secretion of pancreatic juice. This is due to the production of a peculiar substance "secretin," which may be prepared artificially by macerating the duodenal or jejunal mucosa with dilute acids, soaps, and the like (Bayliss and Starling, 1902); or by contact of these or of irritants with the living mucosa. Secretin does not exist as such in the mucosa, but is formed from an insoluble "prosecretin." Secretin is reported to have been isolated as a crystalline compound with picrolonic acid (Hammarsten, Jorpes and Agren, 1933). It is soluble in water and dilute alcohol (70 per cent); insoluble in absolute alcohol, ether, and so forth. It is fairly readily destroyed by acids, alkalis or oxidation, and by the digestive ferments (Carlson *et al.*, 1916).

Actions.—Intravenous injection of secretin stimulates the flow of pancreatic juice, bile (Downs and Eddy, 1919) and succus entericus, but not of the other digestive secretions; nor do extracts of other portions than the small intestines produce the secretory effect. The pancreatic secretion is accompanied, but not caused, by vasodilatation. The pancreas is not readily fatigued, the flow being undiminished after eight hours of continuous injection. Repeated injections of equal doses give identical response. The flow is not affected by anesthesia. Secretin has no effect on sugar metabolism.

The only other direct action of purified secretion, so far as known, is some augmentation of *bile secretion* (Tanturi, Ivy and Greengard, 1937). Secretin increases the *urine flow*, but this is attributed to the intestinal absorption of the fluid from the increased flow of pancreatic juice and bile; it does not occur if these secretions are diverted. It does not require the presence of the hypophysis (C. A. Dragstedt and Owen, 1931).

Gastrin.—Extracts of the pyloric mucosa contain a substance that stimulates gastric and other secretion. This is probably due to histamine, which has been isolated from the extracts (Sacks *et al.*, 1932).

Enterogastrone.—Undigested fat, particularly in the intestines, inhibits gastric secretion and motility. This has been attributed to the formation of an inhibiting hormone, enterogastrone (Kosaka and Lim, 1933). A similar inhibition occurs when dextrose is present in th upper intestines (Quigley and Phelps, 1934).

Cholecystokinin is a powerful stimulant of the gallbladder which has been extracted from the mucosa of the upper intestines. It is much more potent than stimulation of their autonomic nerves. It is active only on intravenous injection and causes prolonged contraction and evacuation of the gallbladder, in man and animals. It may be freed from histamine and choline and seems closely related to secretin. It is probably not identical with it since some preparations may lack either the pancreatic or the cholagogue action. The effect, however, is not greater than that of the ingestion of egg yolks and cream, so that "it is unlikely that it will prove of therapeutic or diagnostic value" (Ivy, review, 1935).

Choroid extract produces a specific increase in the flow of cerebrospinal fluid (Dixon and Halliburton, 1914).

PROTEOSES ("PEPTONE")

Effects of Albumoses.—Intravenous injections of "Witte's Peptone" (0.5 Gm. per kilogram) produce anaphylactoid phenomena (Biedl and Kraus): temporary but considerable fall of blood pressure (Thompson, 1896 and 1899) by peripheral action, in dogs (but not in rabbits, Pissemsky, 1915); stimulation of the isolated uterus (Dale and Laidlaw, 1910); bronchial constriction, peripheral (Baehr and Pick, 1913); increased flow of lymph and secretions (Popielski, 1909); of milk (Ott and Scott, 1912); discharge of the gallbladder (Klee and Knuepfel, 1914); diuresis independently of the blood pressure (Froehlich and Pick, 1912); fever on hypodermic injection, and other effects. In most animals (but not in rabbits) appropriate doses render the blood noncoagulable and produce hyperglycemia and glycosuria (Y. Henderson and Underhill, 1911). McGuigan and Ross, 1917, however, state that the usual result is hypoglycemia, which they attribute to circulatory changes in the liver. The secretion of bile is increased (O'Kada, 1915). Application of peptone to the scarified skin produces a wheal (Sollmann and Pilcher, 1916). Intravenous injection of small doses of pure proteoses greatly increases the urinary nitrogen for several days (Whipple, 1916).

Resemblance to Histamine.—Dale and Laidlaw, 1911, called attention to the striking similarity of the anaphylactic and peptone effects to those of histamine, and suggested that the active principles may be similar. Certain minor differences exist; *f. i.*, epinephrine removes the bronchial spasm of peptone more effectively than that of histamine (Januschke and Pollak, 1911); histamine does not affect the coagulation of the blood (Modrakewski, 1912).

Desensitization.—Dogs that survive "peptone shock" are immune to repeated injections, even of large doses; some 6 per cent of dogs have a natural immunity to "peptone," while neither native nor acquired immunity for histamine exists in dogs (Abel and Geiling, 1924). There is some mutual desensitization between peptone and anaphylactic shock; *i. e.*, each affords some protection against the other (Dragstedt and Mead, 1937).

Sensitization.—On the other hand, it is claimed that the intravenous injection of a small dose of peptone into rabbits produces sensitization, so that another injection results in prompt anaphylactic shock. This sensitization occurs within ten to twenty minutes, reaches its maximum in half an hour and then decreases slowly to complete disappearance in eight days (de Waele, 1923).

Active Constituents.—Typical peptone effects are produced by preparations free from histamine (Hanke and Koessler, 1920) or other foreign toxic admixtures (Underhill, 1903). In dogs, however, some depressor substance, presumably histamine, appears in the blood in peptone shock and also in anaphylactic shock; and it is asserted that the peptone and anaphylactic phenomena are produced by the liberation of histamine from the tissues (Dragstedt, Mead and Eyer, 1938).

Smooth muscle is generally stimulated, similarly to histamine. In *excised intestine*, the stimulation is relatively slight, and inhibition tends to predominate (Olivecrona, 1921). The *bronchial spasm* in guinea pigs is less intense than in anaphylaxis (Loewit, 1913).

Circulation.—The *mechanism of the fall of blood pressure* is identical with that of anaphylaxis (Pearce and Eisenbrey, 1910; Froehlich and Pick, 1912). It occurs when the circulation is short-circuited to exclude the liver, so that the latter is not essential to the fall (Bally *et al.*, 1941). Injection of albumose or histamine into nonanesthetized animals produces flushing of the skin and mucous membranes (Abel and Geiling, 1924). With rabbits, the vessels of the legs and ears are constricted, while the splanchnic vessels are dilated (Kondo, 1919). The excised mammalian heart is weakened by concentrations of 1:1000 to 1:10,000; stimulated by 1:200 (Pissemsky). *Excised vessels* are generally constricted (Dale and Laidlaw, 1911); the ear vessels are constricted by all concentrations; those of the perfused lung are somewhat dilated (Baehr and Pick, 1913); also the liver veins (Berezin, 1914); the intestinal, renal and coronary vessels are unaffected by dilute solutions, constricted by strong solutions (Mautner and Pick, 1915). The effects on blood pressure and respiration were investigated by Zuntz, 1911. Perfusion of Witte peptone through the *liver* produces obstruction of the hepatic veins, probably by vasoconstriction (Simonds and Brandes, 1929). The peptone shock is said to be much less marked in animals whose parasympathetic mechanism has been depressed by *atropine*, and to be greater in those with natural or induced hypersusceptibility of the parasympathetic (Garrelon *et al.*, 1922; Arloing and Langeron, 1922).

"*Hemoclastic Crises.*"—This term was applied by Widal to a clinical syndrome produced by the injection of peptone, by other active colloids, and by anaphylactic reactions. It consists in leukopenia followed by leukocytosis, diminished coagulability, fall of arterial pressure and lowered refractive index of the blood.

Blood Coagulation.—The direct addition of peptone to blood does not affect coagulation; but intravenous injection generally renders the blood noncoagulable. This is due to an antithrombin, the blood containing all the necessary elements for coagulation, so that it clots, *e. g.*, on simple dilution with water. This antithrombin seems to be nucleoprotein formed in the liver (Denny and Minot, 1915). Its production is not increased by bile, bile salts, secretin or electric stimulation. R. J. Lee and Vincent, 1915, attributed the noncoagulability of the anaphylactic blood mainly to an anomalous behavior of the blood platelets.

Effect on Hemorrhage.—Bleeding from superficial vessels is rather increased by the local application of peptone. Intravenous injection may diminish hemorrhage, parallel to the fall of blood pressure (Hanzlik, 1918). Peptone does not agglutinate red corpuscles *in vitro* (Karsner and Hanzlik, 1920). Injections of Witte's peptone were proposed for the treatment of hemophilia, but caused fatal hemorrhage (Leceboullet and Vaucher, 1914).

Lymphagogue Action and Blood Concentration.—Peptone and other shock-producing poisons alter the capillaries so as to produce loss of blood plasma with increase of blood concentration and of lymph flow.

Lesions.—Broughton, 1919, after intraperitoneal injections of Witte's peptone into guinea pigs, describes inflammatory lesions in the liver, heart and kidneys, similar to those produced by other foreign proteins.

Febrile Reaction and Leukocytes.—Intravenous injection of vaccines or foreign proteins is followed by a chill, fever, muscular and joint pains, sweating and a characteristic leukopenia (about the second hour), followed by leukocytosis (fourth hour to several days), sometimes of marked degree (Gow, 1919). The *leukocytosis* is probably associated with the pyogenic reaction, but is not proportional to it. It is chiefly polymorphonuclear. In distinction from anaphylaxis, there is no eosinophilia.

Modified Response to Autonomic Poisons.—Injection of peptones and other proteins, such as milk and sera, and also cholesterol and other colloids, *f. i.*, colloidal metals, modifies the sensitivity to autonomic poisons. Direct addition of peptone to a pilocarpine solution diminishes the augmentor action of the latter on excised intestine (perhaps by adsorbing the pilocarpine), but if the intestine is treated first with doses of peptone that are inactive in themselves, they respond more strongly than normal to the subsequent application of pilocarpine (van Leeuwen and van den Broeke, 1920). In intact animals peptone injections are followed by increased responsiveness of the peripheral autonomic system, for instance to epinephrine and pilocarpine, and this "allergy" persists for a considerable time (Freund and Gottlieb, 1922). Doelken and Herzger, 1922, claim that milk and serum injections modify also the response to strychnine, nicotine, morphine and the like. Gautrelet reports that the injection of peptone (or colloidal silver and other colloids, to a smaller degree), prevents the synergistic hypotensor effect of nigrosine and thionine.

Peptone Injections against Infective Fevers.—Intravenous injection of peptone, in proper dosage, tends to bring on a prompt crisis in various infective fevers and may thus shorten their natural duration. The same result is secured by the intravenous injection of other agents that produce similar reactions—nonspecific bacterial vaccines (for instance, typhoid) or filtered cultures; colloidal metals, and so forth. This treatment has been employed most extensively in acute rheumatic fever. The clinical relief is generally prompt and considerable. Occasionally, however, the reaction is dangerous. The method is not sufficiently safe for promiscuous use.

Nonspecific Protein Therapy.—According to the review of Cecil, 1935, F. Torres was the first to report successful results in the treatment of typhoid fever by intravenous injection of typhoid vaccine. This produced a sharp febrile reaction, followed by improvement. Kraus, Penna and Bonorino, 1917, obtained similar results in typhoid fever by the injection of colon bacillus vaccine, showing that the response is not specific. Lüdke, 1915, also obtained the reaction and improvement by intravenous injection of proteoses, and R. Schmidt, 1916, by intramuscular injection of boiled milk. Various proteins, native and split, are now utilized, as also artificial infection with malaria. The *agents chiefly used* in America are (1) *Cow's Milk as Foreign Protein.*—Sterilized skimmed cow's milk has been used for foreign protein therapy, 5 to 20 cc. injected intramuscularly every day or every second day, generally for three doses. The *reactions* are similar to those of peptone or other colloidal injections: fever (maximum temperature in six to eight hours); sweating; headache; marked local pain, often lasting many hours, but no abscess formation. This "milk disease" differs from "serum disease" by its prompt onset, and by the usual absence of arthralgia and of rashes. Repeated injections of the milk at unsuitable intervals may result in true anaphylaxis (Casson, 1919). The therapeutic use is reviewed by R. L. Cecil, 1935. (2) *Bacterial vaccines*, generally typhoid, diluted with normal saline, intravenously; initial dose, ten to twenty-five million killed bacilli. (3) *Peptone* is adminstered as 10 per cent sterilized watery solution. This is injected intravenously, taking three to five minutes to inject 10 cc. and observing at the same time the pulse and face of the patient. The same dose may be injected subcutaneously. If the first injection is well borne, 10 cc. of 10 per cent solution are again injected on the next day. If the peptone solution enters the tissue around the vein, painful inflammation is likely to result. Intramuscular injections are also followed by considerable pain. Cardiac diseases contraindicate all foreign protein therapy (Nolf and Depage; Jobling). *Excessive reactions* occur if the injection is too rapid or the peptone too active. They resemble anaphylactic shock and consist in marked tachycardia (increase of 30 to 40 per minute), cyanosis, with air hunger, violent headache, nausea, vomiting. They are usually of short duration. Should they occur, epinephrine, 0.5 mg. to 1 mg., may be injected and repeated as needed (Nolf).

Peptone Injections against Allergy.—Since peptone injections tend to prevent anaphylactic shock in animals, they have been tried to desensitize patients subject to bronchial asthma. Good results have been reported also for other nonspecific protein therapy, but they are uncertain (Samter, 1933).

Wound Repair.—Roulet, 1926, claims more rapid healing if 3 per cent aqueous solution of Witte's peptone is injected around the wound.

TISSUE EXTRACTS WITH HISTAMINE-LIKE ACTIONS

Extracts of practically all tissues, but especially of glands and smooth muscle, produce histamine-like or peptone-like effects: stimulation of smooth muscle and glands and fall or rise of blood pressure. Intravenous injection or direct contact are usually required to produce a response. Popielski, 1913, named these principles "*vasodilatin.*" This implies a chemical identity that has not been established. The reactions correspond closely to those of histamine, often with an admixture of choline actions. Both have been isolated, for instance, from lung extracts (Best, Dale *et al.*, 1927) and may suffice to account for the effects. However, other substances may participate: Adenosine derivatives are present in rather large amounts in extracts from traumatized muscle. Felix and Putzer-Reybegg, 1933, reported isolation from mesentery of a crystalline organic depressor base, unidentified but possibly related to guanidine. Inorganic constituents may also play a part: expressed heart juice, *f. i.*, depresses cardiac activity, simply by its potassium content (Macleod, 1907).

Saline liver extract, injected intravenously, produces a fairly persistent fall in blood pressure, analogous to a histamine or a histamine-choline mixture (Burnett, 1926). R. H. Major, 1925, found it effective, intravenously, against experimental guanidine hypertension. It was tried clinically in hypertension and lowered the systolic and diastolic pressure, but about a fourth of the patients showed "reactions" of varying degree and of the usual anaphylactoid type (MacDonald, 1923). A purified extract which does not give chemical protein reactions was prepared by James, Laughton and Macallum, 1926.

Spleen extract stimulates smooth and cardiac muscle similarly to histamine ("*Lienin*") (Rothlin, 1920). Zuelzer, 1908, 1912, introduced an acid extract, "*Hormonal,*" to be injected against intestinal paresis, but its effects were uncertain and sometimes dangerous, even fatal (Hesse, 1913).

The "vasodilatin" of defibrinated blood was studied by Zipf and Wagenfeld, 1930.

Urinary "Hypotensin."—The intravenous injection of urine causes marked fall of blood pressure, similarly to peptone. The properties of a concentrate are described by E. K. Frey and Kraut, 1928.

◆

ALLERGIC PHENOMENA

These present a complex of effects essentially identical with those of histamine and peptone, *i. e.*, stimulation of smooth muscle, and especially bronchial constriction; paralysis of the capillaries with fall of blood pressure and edematous infiltration; hemagglutination; and their secondary consequences. The resemblance is so strong that it points to the fundamental identity of these processes, the differences consisting essentially in the conditions that evoke the effects, rather than in the effects themselves.

The allergic phenomena may be grouped as true anaphylaxis; serum disease; spontaneous hypersusceptibility (food proteins, pollen and bacterial proteins, drug idiosyncrasies); traumatic shock, burns, neurotic edemas; and the anaphylactoid reactions to intravenous injections of colloids, colloidal precipitants, and probably every kind of solution. It is evident that these agencies differ widely in their chemical properties and reactions, and that the allergic effects are quite different from the ordinary actions which these same substances produce by other methods of administration, or in the absence of hypersusceptibility. The allergic reactions therefore seem to depend on something more widespread and less specialzed and more fundamental than the distinctive chemical properties

It has been suggested that the allergic phenomena result from a disturbance of the equilibrium of the colloids, presumably in the direction of a partial condensation, which would tend to alter the surface tensions and to diminish the permeability of cell surfaces, and thus lead to changes in the distribution of water, solutes, and energy. The degree, the rapidity, even the distribution of these changes, and their secondary consequences, would vary and thus account for the differences that relieve the basic uniformity of the allergic reactions. This attractive theory can furnish a plausible explanation for practically all allergic phenomena, but it has not been established by adequate evidence. On the other hand, the differences that exist, according to the conditions that bring about the reactions, are of so much practical importance that it appears advisable to arrange the details under these conditions. An extensive bibiography of allergic phenomena of pharmacologic importance is given by Hanzlik, 1924.

TRUE ANAPHYLAXIS

Parenteral injection of native proteins sensitizes animals specifically, after an incubation period, so that they react violently to a further injection of the same protein; and the excised tissues of such animals are specifically hypersensitive to the sensitizing protein. If the animal recovers from the attack, it is desensitized, *i. e.*, it ceases to respond to further injections. This protection (antianaphylaxis or anergy) is lost in time; as is also eventually the susceptibility of the sensitized animals. The characteristics of true anaphylaxis are its dependence on specific sensitization, with an incubation period; the sensitization of excised tissues; and the relative violence of the reactions. The phenomena of anaphylactic shock differ from those of histamine chiefly by the absence, in the latter, of the changes of temperature, of blood coagulability and of the refractory state (Karsner). These may have little to do with the "shock," but may rather be collateral phenomena.

Historical.—Anaphylactic phenomena were described by Magendie in 1839, and rediscovered by von Behring, 1892; Richet (who coined the name); Theobald Smith, 1903; and von Pirquet, 1905. Their modern investigation dates from Otto, 1905, and Rosenau and Anderson, 1906. The term "*allergy*" (meaning "altered reactivity") was suggested by von Pirquet and Schick, 1906, for the symptoms in man, following a second injection of horse serum, especially the more rapid onset of serum disease.

Production of anaphylaxis results from the parenteral introduction of all "antigens," *i. e.*, all true proteins, but not from their cleavage products, proteoses, leucine, and the like (Gay, 1913); nor from gelatin; nor from lipoids, and so forth. *Artificial polypeptids* (to heptaglycylglycin) do not produce anaphylaxis (Abderhalden and Weil, 1920).

Sensitization occurs with exceedingly small doses as little as 0.000,000,05 mg. of egg white) intravenously or hypodermically, and exceptionally even by stomach or large intestine, or through the nose (Sewall, 1914). A minimum interval of six to ten days elapses before the sensitiveness is acquired; but then it persists for a long time, weeks or years. Repeated injections during the incubation period may produce immunity. The maximum degree of sensitization is practically independent of the dose of the sensitizing injection; but curiously, the maximum is reached more rapidly with small than with large injections; for instance, in guinea pigs with 0.004 cc. than with 0.1 cc. of horse serum (O. Thomsen, 1917) Injection of the serum of sensitized animals confers *passive sensitization* on the recipient (Otto); immediately, with proper dosage (Doerr and Russ). The **provocative injection** must be considerably larger than the sensitizing injection. It is much more effective by vein. The response is immediate. If an animal recovers from the toxic effects it becomes immediately refractory or immune to further injection, because the anaphylactic antibodies are saturated or exhausted (Weil and Coca, 1913). This *antianaphylaxis* (anergy) persists for a time, but is eventually lost. The animal again becomes hypersensitive, and this hypersusceptibility may last for years. **Desensitization** consists in inducing antianaphylaxis by the injection of doses so small that they do not provoke shock. Insusceptibility also occurs if the injections are repeated at intervals of two or three days before the sensitization has developed. This so-called *refractory state* may persist for long periods.

Susceptibility differs markedly in individuals and in species. *Man* seems to be relatively insusceptible. The rare acute accidents in the injection of antitoxic sera, serum disease, and some varieties of asthma and hay fever (Meltzer, 1910) are probably anaphylactic manifestations. *Guinea pigs* are especially susceptible to the respiratory effects, the small lumen of the bronchi being closed by even slight spasm of the bronchial muscles, leading to pulmonary emphysema and asphyxial death in a few minutes (Auer and Lewis, 1909). In *dogs* and *rabbits* this phenomenon is much less marked, the severe and prolonged fall of blood pressure being the most prominent feature. Death may occur, however, by bronchial constriction (Pelz and Jackson, 1918). *Cats* are rather difficult to sensitize. White rats are peculiarly tolerant to anaphylaxis and to histamine (review, C. A. Dragstedt, 1941).

With *white rats*, the second injection of serum must be made within twenty-one days, else the sensitization fades. Acute death is respiratory, but increased capillary permeability is more prominent than muscular spasm. If death is delayed, marked congestion and hemorrhages predominate (J. T. Parker and Parker, 1924). Rats must be at least ten weeks old before they are suitable for anaphylactic experiments. If they are poorly nourished, they cannot be sensitized to anaphylaxis (Weld and Mitchell, 1941).

Share of Tissues in Anaphylaxis.—Anaphylactic sensitization involves mainly the tissues, rather than the circulating blood. Excised and blood-free organs of sensitized animals are highly susceptible to the sensitizing protein (Schultz, 1910); and a sensitized dog transfused with normal blood exhibits immediate anaphylactic shock when the antigen is injected; while a nonsensitized dog transfused with sensitized blood shows no immediate effect when the antigen is injected (Pearce and Eisenbrey, 1910).

Response of Excised Sensitized Tissue.—Foreigln serums generally stimulate the smooth muscle of norma (nonsensitized) animals; but the muscles of sensitized animals respond to much smaller doses of the sensitizing serum, while their reaction to other serums remains unchanged. Dale, 1913, showed that the excised uterus of sensitized guinea pigs is contracted by extreme dilutions of the specific antigen; the production of the hypothetical toxic substance must therefore occur directly in the sensitized tissue. One dose of the antigen desensitizes the excised uterus to further doses (but not to normal serum). The antigen therefore destroys the hypersusceptibility of the sensitized muscles. The persistence of the normal reaction to normal serum is further proof that this is quite distinct from the anaphylactic response. Prolonged contact with serum of a sensitive animal again renders the uterus sensitive (passive sensitization); but a normal utrrus can not be passively sensitized. If the muscle is eerfd from tissue lymph and other diffusible elements by repeated centrifugation in Locke's solution, the sensitiveness is greatly decreased; it is quantitatively restored if these muscles are treated with normal guinea pig serum. This indicates that some constituent of normal serum is essential to anaphylactic stimulation. Direct reactions of the tissue with the antigen have also been observed in the liver (Weil, 1917) and lungs (Manwaring and Crowe, 1917).

The symptoms of anaphylactic reaction are mainly: Great restlessness; severe fall of blood pressure and consequent shock; fall of temperature (Pfeiffer and Mita, 1910); rigidity of the lungs by violent contraction of the bronchial muscles, resulting in respiratory distress and asphyxial convulsions; stimulation of other smooth muscle (uterus, stomach and intestines); hemorrhagic enteritis; diminished coagulability of the blood (Weil, 1917); increased concentration of the blood, appearance of nucleated reds, and changes in the leukocyte ratio (Richet *et al.*, 1919); leukopenia; eosinophilia; loss of complement; increased lymph flow (Calvary, 1911); local inflammatory reaction.

Repeated anaphylactic shock results in cell destruction in several organs, with subsequent chronic inflammatory changes. In the liver, the results resemble the effects of portal cirrhosis. Analogous but less severe *parenchymatous degenerations* of the myocardium, liver and kidneys may occur in rabbits after a *single injection* of a large dose of horse serum or egg albumen. They develop in ten to twenty-one days, about the time when the antibodie are produced (Longcope, 1921).

Lung Rigidity.—Auer and Lewis, 1909, showed that in guinea pigs dying acutely of anaphylaxis the lungs are rigidly distended and incollapsible even after death, by tetanic contraction of the bronchial muscles. The effect occurs after destruction of the central nervous system and after degeneration of the vagi (Auer, 1910). Schultz and Jordan, 1911, showed that the severity of the bronchial phenomena in guinea pigs is explained by their relatively thick mucosa; so that the contraction occludes absolutely even the larger bronchi. Other animals are generally even more susceptible to the bronchial spasm, but its fatality is not so high. Bronchial spasm is also produced on *excised lung*, perfused either through the vessels (Manwaring and Crowe, 1917) or through the trachea (Warnant, 1929), and may be observed microscopically on *lung sections*. These show that the contraction passes off spontaneously if the sections are left in the solution and cannot then be provoked by further addition of the antigen. It is antagonized by epinephrine or atropine (Sollmann and Gilbert, 1937). In *perfused lung*, atropine, epinephrine and ephedrine are moderately effective (Warnant, 1929); and these and nitrites also in intact animals (Pelz and Jackson, 1918; Barlow and Beams), but their efficiency is limited. Roux and Besredka, 1908, claimed that ether anesthesia antagonizes anaphylactic shock in guinea pigs, but all subsequent workers have been unable to confirm this (C. A. Dragstedt, 1935); nor does chloroform relax bronchial contraction in lung sections (Sollmann and Gilbert, 1937). Rosenau and Anderson, 1909, found chloral uncertain in guinea pigs, which probably means ineffective.

Other Pulmonary Effects.—The airway is also obstructed by *acute congestion and edema of the mucosa*, which is quite conspicuous in the larynx. Excised *pulmonary artery* is markedly constricted by addition of the antigen, in contrast to carotid artery which is not contracted (Sollmann and Gilbert, 1938). Coca, 1919, reported the pulmonary circulation of intact guinea pigs unobstructed; but with rabbits dying acutely from anaphylaxis, the pulmonary circulation is almost impermeable to saline, even under pressure several times greater than exists in the pulmonary artery during life. Arrest of the pulmonary circulation would be the immediate cause of death. Coca attributes this to vascular spasm, rather than to plugging by thrombi or agglutinated corpuscles, as had been suggested by Manwaring and Crowe, 1917.

Experimental Asthma by Inhalation of Antigenic Dust.—Guinea pigs so exposed for five to seven hours may develop regional sensitization; subsequent exposure produces marked but more or less extensive regional reactions resembling clinical asthma, without developing antianaphylaxis (B. Ratner, 1939).

Blood Pressure.—In guinea pigs the circulatory changes are mainly asphyxial (Auer and Lewis, 1910). In other animals there is severe fall of blood pressure, often to 20 to 30 mm. Hg. The mechanism of this "anaphylactic shock" has not been conclusively demonstrated, but is presumably the same as with the analogous histamine fall, *i. e.*, direct relaxation of the capillaries. The blood accumulates mainly in the large veins, especially of the liver and portal system, so that the smaller vessels of the kidneys, intestines and other parts of the body are mechanically drained (Edmunds, 1913); indeed, the fall does not occur if the liver has been excluded from the circulation. The liver therefore has a predominant share, directly or indirectly, in the fall. The vasomotor center is not directly involved. The arterioles or veins continue to contract to epinephrine or barium.

Cardiac Disturbances.—The heart suffers by the low blood pressure and is affected directly, although this usually plays a minor part in the "shock." Electrocardiograms show disturbances of conduction and abnormalities of ventricular contraction, affecting especially the right heart. These may progress to final rigor (Auer and Robinson, 1913). The heart muscle and diaphragm show histologic changes; also with other anaphylactoid agents (Kundratitz, 1913). The isolated heart of sensitized animals is directly poisoned by the antigen (Cesaris-Demel, 1910–1912). Acute heart failure is sometimes seen in intact cats (Edmunds, 1914).

Treatment of Anaphylactic Hypotension.—The continued low blood pressure furnishes an opportunity for investigating treatments of shock. The indications are to relieve the splanchnic congestion and to increase the volume of blood to the heart and medulla. Pearce and Eisenbrey, 1910, found that venous transfusion with blood or saline only increases the splanchnic congestion without aiding the heart or medulla. Cardiac or vascular stimulants alone did not produce permanent improvement; but the combination of slow epinephrine infusion with digitoxin gave good results. J. P. Simonds, 1916, found but little pressor response to epinephrine in anaphylactic or peptone shock. Ephedrine also has only a limited success (Chen and Schmidt); pituitary is practically useless. Mautner and Pick, 1915, reported good results from the vasodilator action of nitrites or caffeine.

Physical changes in plasma have been described: flocculation of the plasma colloids, lowering of surface tension of serum, increase of refractometric index of plasma. Flocculation has been demonstrated *in vitro* by incubation of the serum of a sensitized animal with an antigen (Opie, 1923).

The **uterus** is highly responsive to anaphylactic stimulation in most animals. It is not greatly sensitive in rats (Parker and Parker, 1924). The **urinary bladder** is stimulated in guinea pigs, not in rabbits (Manwaring and Marino, 1926).

Localized sensitization, increasing local irritation from repeated local injections of an antigen, constitutes the *Arthus hypersensitivity reaction* (review, A. R. Rich, 1941).

The **susceptibility to autonomic drugs** is not altered by anaphylactic sensitization, in the case of bronchial muscle (Sollmann and Gilbert, 1937) and other organs; except that the guinea pig heart is more responsive to choline (J. Martin and Went, 1939). The anaphylactic state appears to increase the *susceptibility to nonspecific irritants.* When xylene (1 cc.) is rubbed on the ear of normal rabbits it is merely rubefacient; but when the animals have been injected with subsymptomatic doses of an antigen (sensitizing and provocative), xylene produces vesication and eschar (Auer, 1920).

Mechanism of Anaphylaxis.—Since a sensitizing injection of antigen and a following incubation period are necessary to anaphylaxis, change must occur in the body, resulting in the production of the specific antibody which reacts with further injection of the antigen. The identity of the responses indicates that whatever the nature of the antigen, the resulting process is identical. It has been conceived as due to a definite substance, the "*anaphylotoxin*" of Friedberger, 1910, perhaps a product of protein cleavage by a defensive proteolytic enzyme acting somewhat analogous to trypsin (Rocha e Silva, 1941). Since blood-free tissues are highly reactive to the antigen, this substance would need to be formed in each reacting cell. C. A. Dragstedt (review, 1941) showed that *histamine, heparin* and possibly choline are liberated in the tissues, especially the liver, and given off into the blood; the heparin accounting for the noncoagulability of the blood, the histamine for most of the other effects. However, the reaction of agglutinins and precipitins suggests the formation of a deposit of antibody-proteins, specifically modified plasma globulins, on the antigenic surface of the cells (review, P. R. Cannon, 1940). This is in better harmony with the older flocculation theory of Dale and Lumiere, that the anaphylactic phenomena result from the alteration of cell permeability by flocculation or precipitation of the antigen by the antibody, on or within the tissue cells. The antigen-antibody reactions are explainable as chemical *approximation reactions*, such as electronic van der Waals attraction; the *specificity* arising from structural complementariness which permits such close contact of the molecules that weak forces become operative. This explanation is practically that of the Ehrlich lock and key analogy (review, Pauling *et al.*, 1943).

Relative Share of Blood and Tissues.—In passive anaphylaxis the degree of reaction is usually small or even absent if the antigen and antibody are injected simultaneously, and when they would therefore seem to have the best chance of interacting in the blood. The severest reactions occur if the antigen is injected twelve to twenty-four hours after the antibodies—when, in fact, the antibodies have largely disappeared from the blood and are presumably fixed in the tissues. This makes it probable that the reaction occurs more effectively in the tissues than in the blood. There is direct evidence that the union of antibody and antigen is relatively slow in the blood stream; for they may exist there simultaneously and ununited, for days, combining slowly *in vitro* if the blood is removed. This suggests the presence in the blood stream of some inhibiting substance or conditions, such as are common in colloid reactions. It is known that antireactions are inhibited by excess of either antibody or antigen.

Nonspecific Sensitization.—Thienes and Hanzlik, 1926, found that the reactions of smooth muscle are greatly modified by previous treatment with a wide variety of colloids or colloid precipitants.

Treatment of Allergic Intoxication.—The hypodermic injection of epinephrine (1 mg. for man) tends to relieve the bronchial spasm and the edemic phenomena. If it fails, little else can be done, especially if the blood pressure has fallen to shock level. The chief treatment should be prophylactic; the recognition of hypersusceptibility by skin tests; and, if necessary and feasible, desensitization.

Anesthesia on Anaphylactic Response.—General anesthesia by ether is somewhat protective for guinea pigs (A. R. Koontz and Shackelford, 1939), as also urethane and chloralose; but desensitization occurs even when there are no symptoms (L. Farmer, 1937). The mitigation is probably due chiefly to prevention of the release of histamine from the tissues (G. Katz, 1940); but the response to histamine is also diminished by these anesthetics (G. Katz, 1929; Farmer, 1939). Various histamine antagonists (see Index) are being tried.

Injection of *potassium salts* with sheep serum definitely decreases anaphylactic fatality in sensitized guinea pigs. Sodium and thiocyanate ions have no effects (R. G. Carlson and Whitehead, 1943).

ANAPHYLACTOID HYPERSENSITIVITY

This title covers a group of conditions formerly classed as "idiosyncrasies" or "dyscrasias." The subjects respond to small quantities of special substances by more or less violent symptoms of the anaphylactic type, but occurring without antigen sensitization. Accidental sensitization can not be excluded in every case of protein reactions; but the spontaneous reactions are generally distinctive, and many are produced by substances that are not antigens. The following conditions may be counted in this group: asthma, hay fever, serum disease, serum collapse, food idiosyncrasies, urticaria, erythema, eczema, angioneurotic edema, drug idiosyncrasies, "nitritoid" crises. The sensitivity may be *hereditary; i. e.*, there is generally a family history; but it may not become manifest until later in life. It is often not so narrowly circumscribed as true anaphylaxis; *i. e.*, the patient is often hypersensitive to several factors, and one susceptibility may give way to another, from time to time. The serum does not contain specific antisubstances; nor can the susceptibility be transferred by injection of the serum. The subjects can be desensitized, locally or systemically, by graduated injections; but the desensitization is of short duration.

Skin Test of Hypersensitivity.—The human skin is highly sensitive to the capillary poisons and therefore furnishes a useful index of allergic hypersensitivity. Its diagnostic importance in the eruptive fever rests on a similar basis. It is not improbable that this extensive sheet of epithelial cells and the related mucous membranes play an important part in defense reactions.

The specific responses of the skin to local inoculation are of two types, but the difference between them is probably mainly one of degree (Strickler, 1922). (*a*) The urticarial reactions produced by histamine, peptone, and the like; and by the substances to which the subject is hypersusceptible. They consist mainly in edema, with a little erythema and itching, all of short duration. (*b*) Those indicating the presence of an infective agent in the body; for instance, the tuberculin tests. These are accompanied by cellular reactions and are more or less persistent. The skin reactions are a qualitative, but not quantitative, index of hypersusceptibility; *i. e.*, the degree of the systemic reaction is not always proportional to the degree of the skin reaction (Caulfield, 1921). However, in the same individual, changes in susceptibility, for instance, by desensitization, are fairly paralleled by the skin test. The skin may also be desensitized locally (Mackenzie and Baldwin, 1921); but not in the nonspecific urticarias of histamine, and so forth (Sollmann).

Allergenic preparations of N.N.R. are extracts or solutions of substances to which patients may become sensitive. They are used for diagnosis, prophylaxis and treatment; for instance, of pollen asthma.

DRUG IDIOSYNCRASIES

A number of drug idiosyncrasies show striking correspondence with the distinctive characteristics of allergic reactions in general: (1) The possibility of desensitization, which has been described for several of the reactions, but not for all. (2) The idiosyncrasy phenomena do not resemble the ordinary effects of the drug, but belong to the allergic type: urticaria and acute edema of the mucous membranes, asthma, skin eruptions and catarrh, collapse. (3) Very small doses are effective. (4) The hypersusceptibility does not extend to the ordinary actions; for instance, idiosyncrasy to quinine or acetyl-salicylic acid does not increase their analgesic and antipyretic action. The idiosyncrasy may be present on the first use of the drug, or it may develop later.

Drug idiosyncrasies may be arranged under the following types: some of these probably do not belong to the "idiosyncrasy" class, but it seems impossible at present to draw a sharp line. Type 1. *Urticarial* (skin or mucous membranes): quinine, acetyl-salicylic acid, morphine, etc. Quinine and acetyl-salicylic acid can be desensitized. Type 2. *Plant Dermatitis:* Primrose, Ivy, etc. Desensitization reported. Type 3. *Acquired susceptibility to Dermatitis:* procaine? Type 4. *Iodism and Bromism:* variable susceptibility, depending probably on associated irritations. Type 5. *Nitritoid Reactions:* arsphenamine, usually after several injections: dyspnea, cyanosis, suffusion of face. Type 6. *Sympathetic Collapse:* cocaine group, epinephrine. Type 7. *Retinitis:* atoxyl, optochine, aspidium. Type 8. *Hepatitis:* chloroform, phosphorus, arsenic, aspidium.

Sensitization with simple chemical compounds has been reported for arsphenamines, but others were not able to reproduce the results. It has also been reported for primulin and poison ivy (Rackemann and Simon, 1934). Landsteiner and Jacobs, 1935, succeeded in sensitizing guinea pigs to chlorodinitrobenzene, trinitrobenzene and a considerable number of simple benzene derivatives, but a number of closely related substances were negative. Most of the positive substances produce local irritation, and they incline to the belief that some protein compound is produced and that the sensitization is to the denatured protein component (Landsteiner and Chase, 1940). Passive transfer of human hypersusceptibility has been reported to guinea pigs (Bruck, Klausner) for iodine and iodoform and also for diphenylendiamine, but further confirmation is desirable.

"REACTIONS" TO INTRAVENOUS INJECTIONS

The physical conditions and especially the colloid equilibrium of the blood are disturbed by any sudden alterations in its composition, and consequently the intravenous injection of a considerable variety of substances produces anaphylactoid phenomena. Even normal saline solution and transfused blood may produce some "reaction." The degree of disturbance and the violence of the symptoms vary with the nature of the substance, the speed of the injection and the susceptibility of the individual. Generally there is only a brief fall of blood pressure or "nitritoid reaction," or chill; but there may be violent asthma and asphyxial death. As it is not possible to predict the degree of reactions, all intravenous injections imply some risk. Even the milder reactions are undesirable side effects that complicate the therapeutic actions, except in the relatively few instances when they are evoked intentionally.

The *phenomena of intravenous reactions* resemble those of histamine and differ from the ordinary pharmacologic actions of the substances, if these are otherwise active. They generally have little or no action on excised organs, which consorts with the view that the primary disturbance is in the colloidal condition of the blood. They occur without incubation and are not transferable. Hypersusceptibility plays a large part in some, a small part in others. The details of the effects vary with the agents and with conditions, but the difference is in degree more than in kind. The literature is reviewed by Hanzlik, 1924.

Symptoms in Man.—Those of the milder type bear a superficial resemblance to the response to nitrites, and have therefore been called "*nitritoid crises,*" although their mechanism is probably quite different. They consist in excitement and anxiety, flushing of the skin, sweating, precordial distress, tremors, cough and dyspnea; vertigo, headache, nausea, vomiting; chill and fever; joint pains. The serious cases rapidly develop intense asthma, cyanosis, fall of blood pressure, collapse and asphyxial death. The sudden deaths are more commonly caused by colloids and toxins, injected by vein, and sometimes even hypodermically. They are reviewed by Lamson, 1924. The phenomena in animals are essentially similar (Hanzlik, 1924). *Pulmonary distention* is generally present in the fatal cases, at least in animals. Bronchial spasm, however, plays a minor share. More commonly the bronchial stenosis is the result of pressure from pulmonary or peribronchial edema, or from obstruction of the vessels by agglutinated corpuscles or platelets; and in the case of agar, by the coagulated colloid. The type of the bronchial obstruction is rather characteristic of each agent. The *fall of blood pressure* may be due partly to capillary injury, as with histamine; but as edema is generally not very marked, it is probable that other factors are more important, especially the obstruction of the pulmonary circulation by the agglutination. It is conceivable that the heart muscle is also disturbed directly. *Blood changes:* Agglutination of the corpuscles and especially of the platelets is a frequent condition; the carbohydrate colloids produce it even *in vitro* (Karsner and Hanzlik, 1920). The coagulability of the blood is generally diminished and the surface tension is altered.

Causative Agents.—Flocculation of colloids in the blood may result from any agent that tends either to precipitate, or to be precipitated by, blood. The substances reported to produce these effects may be grouped according to their physical characters: (1) *Colloidal Suspensions:* Bacteria and other micro-organisms and vaccines (including faulty distilled water), barium sulfate, camphors, carbon (india ink), fuller's earth, kaolin, oils, resins, etc. (2) *Suspensoid Colloids:* Colloidal metals and metal oxides, arsenous sulfide, dialyzed iron, gold, silver, etc. (3) *Carbohydrate Emulsion Colloids:* Acacia, agar (gelose), pectin, starch, tragacanth, etc. (4) *Proteins:* All kinds more or less. (5) *Toxins.* (6) *Dyes of More or Less Colloidal Character:* Congo red, gentian violet, mercurochrome, etc. (7) *Precipitant Agents:* Acids, formaldehyde, metallic salts, tannin, etc. (8) *Precipitable Substances:* Arsphenamine, especially acid; barium salts, etc. (9) *Crystalloids:* Bromides, iodides, and especially hypertonic solutions; methenamine, glucose, sodium chloride, sucrose, etc.

NORMAL SERUM

In the process of clotting and by changes in the formed elements, serum acquires the property of stimulating smooth muscle. It also provokes other anaphylactoid reactions and may cause true anaphylaxis. Blood serum contains the elements required in the clotting of blood

Its injection sometimes appears to be effective in controlling persistent bleeding in hemophilia, severe anemias, purpura and the like (Weil, 1907). The results, however, are inconstant. There are the same after-effects and dangers as with antitoxic sera: and these dangers must be taken more seriously, since the benefits are more problematical.

Administration as Hemostatic.—Normal horse serum is injected hypodermically, 10 to 20 cc.; the results are said to appear in twelve to twenty-four hours and last one to three months (Richardson, 1908). The intravenous injection of *human serum* or, better, of human blood, is often more effective (Ottenberg and Libman, 1915). In hemophilia, it increases the prothrombin (Addis, 1916).

Smooth muscle is stimulated (Schultz, 1912), as by peptone or histamine, but there are specific differences (Dale, 1913). The proteins of the serum constrict the blood vessels, but do not act on the stomach, intestines and uterus: alcohol extracts of serum dilate the vessels and tend to increase the activity of the intestines and uterus (Clark, 1921). A specific *constrictor substance* is formed in shed blood, probably by changes in the formed elements rather than by clotting (G. N. Stewart and Zucker, 1913). Janeway *et al.*, 1918, found that the vasoconstrictor principle is derived from the breaking up of the blood platelets. It is not a protein, but a water-soluble crystalloid. The vasoconstriction may play a part in hemostasis. The principle which stimulates the *intestine* and *uterus* preexists. With *perfused hearts* (rabbits), Cushny and Gunn, 1913, reported that the addition of serum produces a preliminary stimulation, with stronger and usually faster contractions; and subsequent depression with weakened and slowed contractions, sometimes heart block and eventually arrest. The coronary vessels are constricted. Similar effects are produced by the plasma of the operated animal, by starch solution and other agents.

SERUM REACTIONS

Allergic reactions are of common occurrence in the therapeutic use of serums. They vary widely in type, severity, time of onset, and in frequency, depending on the susceptibility of the patients, the dose, the channel of administration, and the repetition of the injections. They fall into three distinct, though related groups, according to the mechanism of their production: (1) spontaneous hypersusceptibility with immediate reactions; (2) responses to repeated injections; and (3) serum sickness, the normal delayed reaction to a single injection.

The *incidence* depends chiefly on the quantity injected, but about 10 per cent of patients are not disturbed even by large doses. Negroes are said to have relatively low susceptibility. The serum of some horses gives more trouble than that of others.

Spontaneous Hypersusceptibility to Serum; Acute Serum Shock.—Occasionally the first injection of serum produces a violent allergic reaction. The phenomena start promptly, shortly after or even during the injection, but sometimes with a delay, up to half an hour. The milder cases react with a few urticarial wheals, itching, apprehension; the more severe, with generalized urticaria, edema of the face, tongue, throat and bronchial mucosa, presumably bronchial spasm; dyspnea and cyanosis; sometimes collapse and more rarely death. This may occur with relatively small doses of any of the serums, crude or refined. Serious symptoms are recorded in something like 1:10,000 injections of antitoxic serums, death in 1:100,000 (Park, 1913). A history of previous allergic tendencies (asthma, hay fever) can generally be elicited (for instance, in two-thirds of the thirty histories of serum death collected by Gillette, 1909). The spontaneous nature of the hypersusceptibility is also indicated by the fact that the reactions are much more violent than the usual responses of normal subjects to repeated injections.

Treatment.—Epinephrine, 1 mg. hypodermically, should be injected on the first appearance of the symptoms. The addition of atropine, 2 mg., is advisable. The prognosis is bad, and safety consists in the use of proper precautions *before* the serum is injected: inquiry for a history of allergic hypersensitivity (asthma, hay fever, food idiosyncrasies). An endermic test should be made if possible. If positive, desensitization should be attempted, although it is much less effective in man than in guinea pigs. In the absence of a skin test, it is advisable as a routine procedure to inject 0.5 cc. of the serum half an hour before the full dose. Atropine may be injected in advance and epinephrine should always be ready (review, Mackenzie and Hanger, 1930).

Reactions to repeated injections of serum correspond to true anaphylaxis. They vary according to the interval between the injections. If the second injection is given before the antibodies are present in the blood (generally about ten days, but varying in the individual), the "refractory state" of anaphylaxis results; *i. e.*, the outbreak of "serum disease" is postponed for about a week; and so on with repeated injections; although in the end the serum disease may develop, sometimes with apparently increased severity. If the second injection is made after antibodies have been developed, *i. e.*, after some ten days, it provokes a more prompt and more violent reaction than that of normal serum sickness, the degree depending on the quantity of antibodies present, and on the amount of antigen introduced at the second injection. The phenomena range from the accelerated development (two to four days) of mild serum sickness, to alarming, but rarely fatal, asthma and collapse immediately, or within twelve to twenty-four hours (Pirquet and Schick, 1905). Local necrosis may also occur. Practically all individuals are sensitized by therapeutic doses of serum; needless injections of serum should therefore be avoided, although the reactions are generally much less dangerous than with spontaneous hypersensitivity. The anaphylactic hypersensitivity and the violence of the reaction decrease with time: severe immediate reactions occur in two-thirds of large injections made within two months; after three months, there is generally only accelerated serum sickness; after a year, generally only normal serum sickness. The endermic test is likely to be positive for years.

Serum sickness constitutes the "normal serum reaction." It sets in after incubation of usually six to eight days, but is sometimes delayed for two or three weeks.

It starts with swelling of the lymph glands and moderate leukocytosis (later leukopenia), skin rashes, generally urticarial or erythematous, and local edemas, rise of temperature, malaise, gastro-intestinal disturbance, headache and arthralgia, water and chloride retention (Rackemann *et al.*, 1916), but without albuminuria; delayed blood coagulation (Shattuck, 1917). It is sometimes preceded by prodromal sensitiveness and slight redness of the skin at the site of the injection. The condition lasts from one to twenty days.

Treatment.—The urticaria can generally be diminished by epinephrine (1 mg., hypodermically). Netter, 1906, claimed that the rashes are less frequent if calcium chloride is administered: 1 Gm. daily by mouth, on the day of injection and on the two following days. The efficiency appears doubtful.

Mechanism.—The serum reaction appears to be due to the interaction of the antibody (precipitin) with the antigen that is still present in the organism; for the time of onset coincides with the appearance of the precipitin in the blood, and with the outbreak the remaining antigen suddenly disappears from the blood (MacKenzie and Leake, 1921), after which the antibodies continue to increase (Longcope and Rackemann, 1916).

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SPECIFIC SERUMS, VACCINES AND ALLERGIC PREPARATIONS

The immunologic agents used in diagnosis and treatment form a separate and distinct branch of knowledge and could not receive adequate consideration here. They are therefore omitted.

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HISTAMINE ANTAGONISTS

The actions of histamine may be antagonized somewhat selectively by a variety of substances, *benadryl* and *tripellenamide* (*pyribenzamine*) being especially potent. They inhibit the histamine stimulation of smooth muscle and the edema formation, and are useful against allergic reactions, especially urticarial dermatoses, atopic dermatitis, penicillin and sulfonamide reactions, and some other dermatitis. Their effectiveness against hay fever, vasomotor rhinitis and asthma is limited, tripellenamide being apparently more potent. The effect in any case is temporary and palliative, not curative, and they often fail. Both have a high incidence of side reactions, especially sedation and drowsiness, more with benadryl (review, S. M. Feinberg, 1946).

Their potency against histamine and against allergy are not parallel, an argument against the histamine theory of anaphylaxis (W. Jadassohn *et al.*, 1944). The *Fourneau substances 929 F and 1571 F* antagonize histamine stimulation of smooth muscle, but not of gastric secretion (Bourque and Loew, 1942). They are fairly effective, but are too toxic for clinical use. The newer French compounds, *antergan* and *neoantergan*, are chemically related to benadryl and tripellenamide (Feinberg). Various *amino acids* (arginine, histidine, cystine) block the histamine action on excised smooth muscle, but only with large doses which are probably not attained in the body (Rocha e Silva, 1944). These also inhibit anaphylactic contraction of excised intestine (Landau and Gay, 1944).

Benadryl, beta-dimethylaminoethyl benzhydryl ether hydrochloride, "S 51," is reported the most potent of the known histamine antagonists (W. A. Selle, 1946). It also antagonizes acetylcholine, like atropine (E. R. Loew *et al.*, 1946). Intravenous doses which have little direct effect on the *blood pressure* of dogs, inhibit the pressure fall of histamine and of acetylcholine, increase the pressor response to epinephrine, stimulate respiration, decrease duodenal motility, and have no effect on the uterus (Sherrod *et al.*, 1946). *Large doses* cause a sharp fall of blood pressure, arrest of respiration and decreased pressor response to epinephrine, histamine and barium chloride (I. H. Page and Green, 1946).

Benadryl relieves the fatal *bronchial spasm* induced in guinea pigs by atomized histamine (Loew, Kaiser and Moore) and by anaphylaxis; partially the histamine fall of blood pressure and the intestinal spasm of barium and acetycholine. It also antagonizes the secretory stimulation of histamine (E. R. Loew *et al.*, 1946). With intact dogs it is more effective than its dipropyl homolog "S 82" (F. W. Ellis and Newsome, 1946). The blood pressure antagonism to histamine is directly proportional to the dose; the curve suggests that benadryl is adsorbed at the same site as histamine and so competes with it (J. A. Wells *et al.*, 1945), but this lacks direct proof.

Clinically, it is often, but not always, effective against hay fever, acute or chronic urticaria and various spasms of smooth muscle. It may be administered by mouth (50 to 100 mg. one to five times daily) or hypodermically (A. C. Curtis and Owens, 1945). There is a wide margin between the therapeutic and toxic dose, but minor side actions are common: sleepiness, dizziness, dry mouth, nausea, weakness, nervousness, mental lethargy, confusion, rarely neuritis (reports, J.A.M.A., 1947, *133:* 392).

Tripellenamide (*Pyribenzamine*) **Hydrochloride,** N.N.R., pyridyl-benzyl-dimethylethylenediamine hydrochloride, "63 C," counteracts the effects of histamine and anaphylaxis. It potentiates epinephrine against human bronchial asthma (Koepf *et al.*, 1946). It enhances the pressor action of epinephrine and stimulates uterine and duodenal motor activity. In contrast to benadryl, it does not inhibit the acetylcholine fall of blood pressure. It produces analepsis and local anesthesia (Yonkman, Chess *et al.*, 1946). It occurs as white stable crystals, nonhygroscopic, readily soluble in water (130 Gm. in 100 cc.), with practically neutral reaction. It is marketed as tablets of 50 mg. The dosage may start with 50 mg. by mouth, four times daily, after meals. If this is effective, smaller doses should be tried; if it is ineffective, the dosage may be increased progressively to 150 mg. four times daily. Its side actions are similar to those of benadryl. Homologs "2786 RP" ("*antergan*") and "2339 RP" have almost quantitatively identical actions (Sherrod *et al.*, 1946; W. Ramanamanjary, 1944; Bonvallet and Decourt, 1944). W. H. Feinstone *et al.*, 1946, describe the histamine antagonism of a new pyrimidine compound, *hetramine.*

Antispasmodic properties of substituted *phenylpropyl piperdines* are reported by T. J. Becket *et al.*, 1946.

Benzofuranone derivatives (*amethone*) have antispasmodic actions, with a potency for rabbit's ileum of about a tenth that of atropine against acetylcholine, and twice that of papaverine against barium chloride. They antagonize histamine bronchiolar spasm and tend to prevent anaphylactic shock (R. K. Richards, Everett and Kueter, 1945).

Aldehydes, formaldehyde, acetaldehyde, paraldehyde, aldol and acetophenone, in fairly low concentrations, relax histamine contraction of the guinea pig intestines and uterus. Carbohydrate aldoses and ketoses do not share this action (A. I. Kendall, 1927).

Histaminase (marketed as "*torantil*") has been proposed for the treatment of allergy, with the hope of destroying the histamine. The clinical results are equivocal (review, Rackemann, 1940), and it fails to modify histamine shock (B. Rose and Browne, 1941) and anaphylactic shock (A. F. Knoll, 1940). Histaminase (diamine oxidase) is not the only, and perhaps not the principal, agent of histamine destruction in the tissues (B. Rose, Karady and Browne, 1940).

Histamine injections do not result in tolerance. Injection of *histamine-azo-protein* has given questionable results.

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BLOOD COAGULATION

Mechanism of Coagulation.—The pertinent facts of blood coagulation may be described in terms of several rather complicated and conflicting theories. Briefly, the coagulation consists in the transformation of the dissolved *fibrinogen* of the circulating blood into insoluble *fibrin* by the action of *thrombin* (fibrin ferment). *Fibrinogen* is an acid globulin, formed exclusively in the liver (Foster and Whipple, 1922). *Thrombin* is not contained in the circulating blood, but is formed from prothrombin by the action of thrombokinase, which requires the calcium ions present in the blood. Thrombin is a protein, probably a hydrolytic cleavage product of prothrombin, perhaps itself a proteolytic enzyme, for it converts 2000 times its weight of fibrinogen into fibrin. Its properties are similar to those of trypsin (J. H. Ferguson, 1943); other proteolytic enzymes, papain and snake venom, may take its place in coagulation.

Prothrombin has the properties of a globulin, composed of two fractions, A and B (A. J. Quick, 1943). Both are formed in the liver (F. L. Munro *et al.*, 1945). The plasma normally contains about 40 mg. per 100 cc. Its activation by thrombokinase appears to consist in cleavage into smaller albumin molecules (Astrup and Darling, 1942). *Thrombokinase* (*thromboplastin, zymoplastic substance*) is a lipoprotein closely allied to cephalin. It is furnished by the disintegration of the tissue elements, blood cells, blood platelets and injured tissue cells over which the blood has flowed. It consists of impure cephalin or cephalin protein compounds. Blood coagulation gives rise to vasodilating substances, apparently compounds of adenylic acid and later to vasoconstricting substances which stimulate smooth muscle (review, A. J. Quick, 1944). *Reinjection of the defibrinated blood* of a rabbit is fatal, but not if it has stood fifteen to thirty minutes. The toxicity is probably due to thrombin (Lenggenhager, 1936). Thrombokinase is inactivated by incubation with plasma (L. M. Tocantins, 1943).

The prevention of intravascular coagulation is attributed to the continuous production of several anti-substances, especially *antithrombin*, associated with the albumin fraction, similar to hirudin, which prevents the action of thrombin on fibrinogen; and *antiprothrombin*, similar to heparin, which holds prothrombin in inactive combination. The addition of citrate or oxalate to shed blood prevents coagulation by inactivating the calcium. *Hemophilia* involves deficiency of thrombokinase, apparently by abnormal stability of the blood platelets (Birch, 1931). *Purpura vera* is characterized by a decreased number of platelets. *Decrease of fibrinogen* occurs in the severe hepatitis of phosphorus or chloroform poisoning, and after repeated bleeding or other blood dilution.

Diagrammatic Synopsis of Blood Coagulation Factors: Fibrinogen + thrombin → fibrin.

Prothrombin + calcium ions + thrombokinase → thrombin.

Thrombokinase = cephalin; brain, lung and tissue extracts.

Antithrombin, hirudin, colloid dyes: inhibit action of thrombin on fibrinogen.

Antiprothrombin, heparin: prevent conversion of prothrombin.

Peptone, anaphylaxis: promote formation of heparin.

Dicumarol: inhibits formation of prothrombin.

Vitamin K, menadione: promotes formation of prothrombin.

Biliary deficiency: prevents absorption of natural vitamin K.

Hepatitis: produces fibrinogen deficiency.

Hemophilia = thrombokinase deficiency.

AGENTS PROMOTING BLOOD COAGULATION

Vitamin K: Naphthoquinone Derivatives.—Deficient income or absorption of this vitamin lowers the prothrombin content of the blood and disposes to hemorrhages and ecchymoses, first observed on chicks, and confirmed in certain clinical conditions, especially in biliary obstruction, since bile salts are necessary to the absorption of the natural substance. The hemorrhagic tendency is promptly remedied by the oral administration of the vitamin, together with bile salts if bile is also deficient.

H. Dam, 1935, noted a hemorrhagic tendency and slowed coagulation time in chicks, due to deficiency of prothrombin, and curable by the administration of certain fat-soluble extracts from putrid fish meals, from liver and alfalfa (Almquist and Stokstadt, 1935; S. A. Thayer *et al.*, 1937). The protective substance, which Dam named vitamin K, is present in other leaves, tomatoes, egg yolk and other foods, so that deficiency is not likely to occur in human diets. Green leaves are probably the richest natural source. It is most abundant in the photosynthesizing parts of plants (review, H. J. Almquist, 1941). It can also be synthesized by bacteria. It has been identified by Dam and Karrer, 1939, by Doisy *et al.*, 1939, and by L. B. Fieser, 1939, as ethylphythyl naphthoquinone, and named *phylloquinone* or *phytoquinone*. Two naturally occurring forms have been isolated, K_1 and K_2. Various *other naphthoquinone derivatives* have the same action; for instance, "*phthiocol*," 2-methyl-3-hydroxyl-1,4-naphthoquinone (Almquist and Klose, 1939); hydroxy naphthoquinone, and especially *menadione, 2-methyl-1,4-naphthoquinone*. which is three or four times more potent than the K vitamin because it is more rapidly absorbed (Ansbacher and Fernholz, 1940). The potassium salt of its disulfuric ester is readily absorbed from the intestines even in the absence of bile, nor do bile salts hasten its absorption (E. D. Warner and Flynn, 1940).

Actions.—Vitamin K and the related naphthoquinone derivatives stimulate the liver to the production of prothrombin, which is used up in forming fibrin. The potency may be *assayed* by the method of Thayer and Doisy, 1938. It counteracts dicumerol if adequate doses are used (Cromer and Barker, 1944). The naphthoquinones, like other quinones, interfere with oxidative chain reactions and are potent bacteriostatic agents for both gram-positive and gram-negative bacilli (Colwell and McCall, 1945). No *toxic effects* are produced in mammals by menadione in doses corresponding to 125 times the maximum clinical dosage per weight (S. Ansbacher *et al.*, 1942). The fatal dose for dogs is 110 mg.; for rabbits, 120 mg.; for mice, 500 mg.: all per Kg. of body weight. Half of this, or prolonged administration, produces marked anemia. High doses cause hyperprothrombinemia (R. K. Richards and Shapiro, 1945; Molitor and Robinson, 1940).

Vitamin K deficiency occurs in adults chiefly through interference with its absorption, when sufficient bile salts do not reach the intestines in obstructive jaundice and biliary fistulas (Quick *et al.*, 1938; Brinkhouse *et al.*, 1938; review, Howell, 1945); in severe intestinal disorders; and to some degree by the use of mineral oil laxatives (Javert and Macri, 1941). Extensive injury of the liver prevents the formation of prothrombin even with ample vitamin K supply and absorption. Prothrombin deficiency cannot be produced in adults by diets poor in vitamin K, since adequate amounts are synthesized by the intestinal bacteria. Sulfonamides interfere with the formation (A. Kornberg *et al.*, 1944). In *newborn infants* the bacterial source is not available until the intestinal flora becomes established. Meanwhile their prothrombin content falls progressively during the first three days after birth (H. N. Sanford *et al.*, 1942). This may be prevented by administering the vitamin or 1 mg. of menadione, either to the mother four to ten hours before parturition, or to the child for several days (Mull *et al.*, 1941); but it is not established that this decreases the incidence of postnatal hemorrhagic conditions.

Clinical Use.—Hemorrhagic conditions are likely to arise when the prothrombin level of the blood falls below a third of the normal. If the fall is due to deficient vitamin K income or absorption, the deficiency may be corrected by administering vitamin K with bile, or the related naphthoquinones. They counteract the prothrombin fall of intensive salicylate administration (R. K. Richards and Shapiro, 1945). They would not be effective against hemorrhagic conditions in which prothrombin is not decreased, such as purpura and hemophilia (review, Snell and Butt, 1939).

Administration.—Menadione, 1 to 4 mg. by mouth (Roads and Fliegelman, 1940), has the advantage that bile is not necessary for its absorption. It may also be administered intramuscularly in oil (Tage-Hansen, 1939), or by vein if necessary (J. H. Olwin, 1941). A single injection of 2 mg. in 20 cc. of isotonic saline keeps up the prothrombic level for at least four days. It may cause brief local pain, but is not toxic and does not injure the liver; the presence of liver damage, however, interferes with its action (J. W. Norcross and McFarland, 1940).

Menadione, 2 mg. daily during the last week of pregnancy, prevents hemorrhagic diseases of the newborn due to prothrombin deficiency.

***Menadione,** U.S.P., 2-methyl-naphthoquinone (menaphthene, menaphthone): a bright yellow crystalline powder, nearly odorless, slightly soluble in water, soluble in organic solvents and in oils, irritating to respiratory tract and skin. The alcoholic solution is vesicant. *Dose,* 1 to a maximum of 2 mg. daily, for not longer than four weeks. In biliary deficiency, bile or bile salts should be administered. *Menadione tablets,* U.S.P.; usually available as 1 mg. *Menadione Sodium Bisulfite,* U.S.P., replacing the 4 oxygen with $OH.SO_3Na$, and containing about 50 per cent of menadione, is soluble in water (1:2). It is used in *Menadione Sodium Bisulfite Injection,* U.S.P., in water for injection. *Dose,* intramuscularly or by vein, 2 mg.; usually available as ampuls of 2 mg. in 0.5 cc. or 4 mg. in 1 cc.

Vitamin K_1, N.N.R., 2 methyl-3 phytyl-1,4-naphthoquinone, is isolated from natural sources or prepared synthetically. Its effect is perhaps more prolonged than that of menadione. It is insoluble in water; soluble in organic solvents and vegetable oils. *Dose,* 4 to 10 mg. by mouth, with or without bile salts.

Phthalic acid has a marked antihemorrhagic effect on rats with ligated bile ducts (Kudriashev, 1943), and lowers the prothrombin time in dogs treated with dicumerol (Jaques and Dunlop, 1945). It does not have vitamin K effects on chicks (H. Dam, 1943).

Cephalin and thromboplastic tissue extracts were introduced to check capillary hemorrhage, by packing with compresses saturated with the solution. Their value is questionable, since the traumatized tissue itself furnishes them in abundance, even in hemophilia. Intravenous injection is dangerous and subcutaneous injection is ineffective. N.N.R. lists several *Brain Extracts* and a *Lung Extract.*

Occurrence.—Cephalin is closely related to lecithin, differing only by a methyl group (Koch and Woods, 1905), but lecithin does not hasten coagulation. Cephalin is widely distributed in the body, so that coagulant extracts can be prepared from all tissues. It is especially abundant in the brain, and "thromboplastins" are generally prepared from that source. Mills believes that the cephalin of other organs is combined with protein into more active "tissue fibrinogen." Such extracts, for instance from fresh lungs, produce intravascular coagulation when injected into the blood stream (Fischl, 1916; Mills, 1919), while cephalin does not produce this effect.

Systemic Phenomena.—*Brain extracts* produce anaphylactoid phenomena on injection, and agglutination of red corpuscles *in vitro;* but pure cephalin lacks these effects (Karsner and Hanzlik, 1920). *Extracts from fresh lung* kill promptly by intravascular coagulation (P. Morse, 1920).

Calcium ions hasten the conversion of prothrombin into thrombin, but changes of calcium ions sufficient to affect this in either direction would be incompatible with life (Crane and Sanford, 1937).

Various substances have been administered by mouth to increase the coagulability of normal blood, in aneurysm and gastric ulcer and other chronic internal hemorrhages. Tainter, Throndson and Richardson, 1939, confirmed that *gelatin* (to 45 Gm. per day), fibrinogen and histidine do not alter the coagulation time.

AGENTS THAT IMPEDE BLOOD COAGULATION

Heparin is the name applied by Howell and Holt, 1918, to a purified liver extractive which prevents the coagulation of blood when a small quantity, less than 1:100,000, is added (W. H. Howell, 1928), or when it is injected into a vein (10 mg. per Kg.). In man, 100 mg. prolonged the coagulation time to three times the original, returning gradually to normal in about two hours (Hartman and Mason, 1924). It is produced and stored by the basophilic mast cells which are scattered generally along the walls of the small vessels, especially of the veins and intercapillary spaces. Glisson's capsule of the liver is rich in these cells, but lung tissue is even richer and is a better source of heparin (C. D. Snyder, 1942). Crystallized heparin is a mucoitin polysulfuric acid ester, consisting of equimolecular parts of glycuronic acid and acetylated glycosamine (E. Jorpes, 1939; Charles and Scott, 1940). It is strongly acidic and forms stable salts with proteins, in stoechiometric proportions (L. B. Jaques, 1943). Heparins from various species differ materially in potency without detected chemical difference (Jaques *et al.*, 1942; review, W. H. Howell, 1941; A. J. Quick, 1944).

Actions.—Heparin antagonizes thrombokinase, preventing the conversion of prothrombin into thrombin. It is not itself antithrombic, but with a cofactor present in serum albumin it inactivates thrombin (J. H. Ferguson, 1937). It prolongs the clotting time, but not the prothrombin time. It inhibits proteolysis of casein by crystallized trypsin, and the destruction of thrombin by trypsin or protease (Gazko and Ferguson, 1940). It prevents the agglutination of platelets (probably by its anticoagulant action; Bürker).

Heparin injection does not materially prolong the duration of hemorrhage (Hartman and Mason, 1924), presumably because the thromboplastic action of the tissues is stronger. Intravenous injection has no effect on the blood pressure and respiration, provided the heparin is adequately purified; otherwise there may be violent reactions.

Heparin is concerned in maintaining the normal fluidity of the circulating blood (Howell). In peptone and anaphylactic shock, its blood concentration is increased, diminishing the coagulability (Jaques and Waters, 1941). It inhibits the release of histamine by trypsin, protease or specific antigens, from the blood cells to the plasma (C. A. Dragstedt *et al.*, 1942). *Salmine sulfuric acid* (a protamine) neutralizes the effect of heparin *in vivo* and *in vitro.* Intravenous injection immediately arrests excessive bleeding from heparin (Jorpes, Edman and Thaning, 1939).

Fate.—The effect of heparin on intravenous injection is prompt, but not sustained. The excess disappears rapidly from the blood. Urinary excretion reaches a peak in twenty to fifty minutes and accounts for 10 to 35 per cent of the injected dosage (Copley and Schneedorf, 1941; J. E. Jorpes, 1943).

Clinical Use of Heparin.—This is employed as anticoagulant in *blood transfusions.* Its addition to drawn blood has no advantage over citrate; but it may be injected by vein into the donor, 1 mg. per Kg. of body weight (or 1.5 cc. of 5 per cent per 75 Kg.), without toxic effects to donor or recipient (even with 10 mg. per Kg.). It lengthens the clotting time immediately, but its potency varies with individuals (Sappington, 1939). Its chief indication is for the *prevention of thrombosis* (C. H. Best, 1938; G. Murray, 1940), after operations, especially in blood vessel surgery, in vascular disease of the brain, coronaries and central vein of the retina, in polycythemia, and in frost-bite (K. Lange *et al.*, 1945).

Intravenous administration should be started three hours after completing the operation and continued until the patient can move actively in bed. Hypodermic injection is less suitable (L. B. Jaques, Charles and Best, 1938). Heparin and dicumerol may be used jointly, the latter for more lasting action. Neither agent dissolves clots that have already formed. The effects must be carefully controlled by coagulation and prothrombin time, as overdoses may result in serious hemorrhage. Penicillin increases the effect of heparin in variable degree, sometimes fatally (Hines and Kessler, 1945).

Heparin solution is marketed in 10 cc. vials, 10 mg. per cubic centimeter; one cc. keeps 5000 cc. of plasma liquid for four hours at 37° C. It is generally administered in normal saline by intravenous drip, 20 to 30 mg. in twenty to sixty minutes. The action may be prolonged by intramuscular injection of a beeswax mixture (Bryson and Code, 1944).

Other anticoagulants which are useful in the laboratory are less suitable for clinical use; hirudin, because of low potency and limited supply; dyes and the other agents, because of the generally narrow margin between the effective and toxic doses (review, Prandoni and Wright, 1942).

Hirudin.—The cervical glands of the common leech (Hirudo) secrete a substance (hirudin, hemophilin) which delays or hinders the coagulation of blood inside and outside the body, by preventing the action of thrombin on fibrinogen. This substance is not destroyed by boiling or by alcohol. It appears to be a deutero-albumose. The leech secretion also contains a histamine-like substance which produces capillary dilatation and increases the bleeding (B. A. Lindemann, 1939).

Therapeutic Use.—Leeches were at one time used extensively for the abstraction of blood in local inflammations. Dry or wet cupping was then substituted, but they are still employed occasionally; two to four of the animals are applied. Each leech draws from 5 to 7 cc. of blood. It is sometimes difficult to stop the bleeding. For experimental use, an extract may be prepared when needed, by crushing the leech heads with sand, macerating with saline for two hours, and centrifugalizing. Each kilogram of animal requires the heads of three leeches, extracted with 3 cc. of normal saline. The solution loses activity on standing, more slowly in the cold.

Immunization.—Daily intravenous injection of hirudin into mice creates an anticoagulant substance, effective *in vivo* and *in vitro*, destroyed at 65° C. It also inactivates fluorides, but not the calcium precipitants. The mechanism of its action has not yet been explained (Vera and Leo Loeb, 1914).

Toxic Effects.—Fresh preparations may be injected intravenously in sufficient quantity to render the blood noncoagulable, without damage to the animal. Some commercial samples of hirudin, however, are highly toxic, especially to dogs, probably through the presence of putrefactive bases. The symptoms from 20 to 25 mg. per kilogram in dogs consisted in severe bloody diarrhea and continued vomiting, with hemorrhagic lesions of the viscera (Marshall, 1915). Engelmann, 1911, injected 0.3 Gm. into a number of eclamptic patients intravenously with and without toxic symptoms. Small quantities were also used in the transfusion method of Satterlee and Hooker, 1914. Lewisohn, 1915, obtained alarming symptoms after 0.1 Gm. of Hirudin-Sachsse.

Dicumerin (Dicumerol).—Oral administration of this substance inhibits the formation of prothrombin. Its effects do not become manifest until the stock of prothrombin has become exhausted, in about forty-eight hours. It greatly prolongs coagulation and prothrombin time, impairs clot retraction, and increases the sedimentation rate of erythrocytes. It is otherwise practically nontoxic.

It is the causative agent of "*sweet clover disease*," a fatal hemorrhagic condition which occurs in cattle fed, on spoiled melilotus hay or silage (reviews, A. J. Quick 1944; Prandoni and Wright, 1942).

Chemical.—Dicumerol, 3.3′ methylene-bis(4-hydroxycoumarin), is formed from the coumarin that exists in the plant. It was isolated by K. P. Link *et al.*, 1940, and synthesized by Stahmann, Huebner and Link, 1941. Many derivatives are similarly anticoagulant, but are less potent (Link, 1945). It is only slightly soluble in water, but forms soluble salts with alkalis. Rather high alkalinity (beyond *p*H 8) is necessary to keep it in solution. It is readily absorbed from the alimentary tract.

The *prothrombin level* of the blood is lowered slowly by a single dose of dicumerol, reaching a minimum in forty-eight to ninety-six hours, then gradually returning to normal in about a week. A critical minimal dose is necessary; increase of the dose above this does not hasten the prothrombin fall (Quick, 1943). A single dose of 3 to 5 mg. per Kg. for rabbits may lower the prothrombin by 80 per cent (Roderick, 1931; Quick, 1937; Overman *et al.*, 1942). Daily repetition for twenty days lowers it to 10 per cent without marked deleterious consequences.

The effects do not result in permanent injury if they do not go too far, and the usual doses do not appear to produce other toxic actions. Coagulability is restored by discontinuing the administration or by injecting normal serum or blood. In contrast to heparin, it has no effect when added to blood *in vitro* (reviews, Quick, 1944; Prandoni and Wright, 1942).

Toxic Effects.—More prolonged administration, or a single intravenous injection of 250 mg. per Kg., results in dangerous and fatal hemorrhages into various organs, especially at points of stress in the subcutaneous tissue and intramuscular fascia, and into the gastro-intestinal tract, pleura and lung (C. L. Rose *et al.*, 1942). Capillaries, arterioles and veins are widely dilated (Bollman and Preston, 1942). Central liver necrosis may develop, probably secondary to the local bleeding, if the animal does not die from the hemorrhages or from pulmonary edema. High levels of ascorbic acid may partly counteract moderate levels of dicumerol (review, K. P. Link, 1945).

The *mechanism* by which dicumerol lowers the prothrombin level is not established, but probably consists in inhibition of the enzymatic reactions that produce prothrombin, perhaps inability to utilize vitamin K; but it can be antagonized by administering excess of K vitamin. It also affects the fibrinogen level; this tends to be lowered by large, and raised by smaller, doses (U. D. Irish and Jaques, 1945). It inhibits platelet agglutination (M. Spooner and Meyer, 1944) and so tends to prevent thrombosis.

The clinical indications of dicumerol are as prophylactic against intravascular clotting in postoperative thrombophlebitis and embolism. Oral administration tends to prevent venous thrombosis, for instance after ligation of a vein or injection of a sclerosing agent. It may be useful in endarteritis. It does not take the place of heparin in urgent conditions, but is useful for prolonged action. It does not dissolve formed clots (R. K. Richards and Cortell, 1942; Stafford *et al.*, 1943; H. D. Zucker, 1944).

The *dosage* must be controlled by daily determinations of prothrombin. About 0.3 Gm. may be administered orally on alternate days (Stats and Bullowa, 1942; Overman *et al.*, 1942). Rectal administration in theobroma suppositories is sometimes fully effective, but is not reliable (O. O. Meyer and Spooner, 1943; O. Wilander, 1938).

Other Anticoagulant Agents.—Intravenous injection of *Witte's peptone* (0.3 to 0.6 Gm. per Kg.) acts by stimulating the formation of heparin (Quick, 1936). Various *azo-dyes* are used in experiments on animals, especially Chicago Blue 6 B, Niagara Sky Blue, Chorazol Sky Blue and Chlorazol Fast Pink BKS; also an amine dye, Pontamine Fast Pink.

The clotting time is not lengthened, but rather shortened, by intravenous injection of sodium oxalate, or intramuscular sodium citrate (J. A. Richardson *et al.*, 1941).

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ANIMAL VENOMS

Various animals form toxic substances belonging to different groups. They are reviewed by H. E. Essex, 1945.

Snake Venom.—About a sixth of the known species of snakes are venomous, all in orders of Colubridae and Viperidae. Their salivary secretion contains a complex of toxic substances, the most important being proteoses, some with enzyme actions. The proteose is largely responsible for the systemic, the protease for the local actions (Houssay, 1923). They are related to the venoms of bees, spiders and scorpions. E. Faust attributed the actions to non-nitrogenous sapotoxin-like substances, but these have not been confirmed (review, O. Gessner, 1938).

Local actions predominate with some venoms, systemic effects with others. Most venoms produce intense cellulitis at the site of the bite, with marked ecchymosis and swelling, and sometimes gangrene. They generally affect the *blood* profoundly, some increasing and others decreasing the coagulability (Hanut, 1939). Several cause hemolysis. Many lower the blood pressure similarly to histamine. The leukocytes may decrease to 25 per cent of the normal count.

The *systemic actions* are nervous, and mainly central. The most conspicuous is a bulbar paralysis. There is a period of incubation (in man, of about four hours' duration); the patient then becomes drowsy, and then presents an ascending paralysis of the cord—*i. e.*, in the order of legs, arms, larynx and tongue. This may be preceded by convulsive movements. There is also salivation and vomiting. The *respiration* becomes dyspneic, giving rise to asphyxial convulsions and forming the cause of death. The fatal dose of rattlesnake venom for man would be about 0.15 to 0.3 gm., hypodermically. The heart beats for some time after the respiration stops. *Vascular paralysis* leads to fall of blood pressure, partly by direct proteose action, partly by liberation of histamine (Kellaway and Feldberg, 1937). Direct cardiac injury has not been demonstrated. *Blood coagulation* is accelerated by many viper venoms and by some colubrides. It is attributed to cytolysis of platelets and increase of thrombin. It has been suggested for the treatment of hemorrhage, but is not superior to less toxic hemostatic agents. Cobra venom inhibits blood coagulation, its protease destroying the fibrinogen (W. Billing, 1930). Excised *smooth muscle* is generally contracted in a manner similar to but not identical with histamine (C. H. Kellaway, 1929). *Curare-like effects* are produced by nearly all snake venoms, more with cobra than with vipers. They appear more potent in living animals than in excised muscle, and are responsible for the fatal arrest of respiration. They are not antagonized by physostigmine (Yagi, 1918) and are not reversible except by antitoxin (Kellaway, 1932). Snake venoms have no effect on infusoria, bacteria, or on plants, but they are toxic to all animals above the hydra.

The *danger of snake bite* depends on many conditions. The actual *mortality* in the United States is about 16 per cent without treatment, 3.75 per cent with antitoxic serum. In East India, the annual deaths are said to be 20,000 to 25,000 persons (R. Hutchison, 1930).

The treatment of snake bite must be prompt. The specific *antisera* are effective, and as they are not strictly specific, polyvalent and even nonspecific antivenom sera are useful (Kellaway, 1930). The antitoxins remain potent for a long time if properly kept. Local measures directed to slowing the absorption of the venom, or to its chemical destruction, are of questionable value, even if used immediately, and quite useless if there is any delay. These include ligation, expression, suction, cauterization and excision of the site of the bite; rubbing with crystals of potassium permanganate, or hypochlorite or iodine solutions. These agents are liable to do more damage to the tissues than to the venom, under practical conditions, although they detoxicate it *in vitro*, as do also formaldehyde, soaps, and bile (O. Gessner, 1938). Blood transfusion may be useful to the depressed circulation. Analgetics and sedatives, barbiturates, morphine and the traditional alcohol, help to relieve the pain and fright. Strychnine is harmful.

Cobra (Naja) venom, injected intramuscularly in minute amounts, is reported to produce marked central analgesia, resembling that of morphine, but devoid of addiction and withdrawal phenomena (Calmette, 1933; Taguet, 1933; Macht, 1936, 1938). It has been employed against severe intractable pain, in malignant conditions, tabetic crises, angina pectoris, tic douloureux, Parkinson syndrome and arthralgias. Blind tests in comparison with saline injection indicate a limited efficiency, but it may be completely ineffective (D'Amour and Smith, 1941; Talkov and Bauer, 1943). Some hours may elapse before the action is apparent. It is probably neurotoxic. It may cause severe side actions, nausea and vomiting, diarrhea, pain at the site of injection, sometimes very intense (Steinbrocker *et al.*, 1940; preliminary report, Council on Pharmacy and Chemistry, 1940, J.A.M.A., *115:* 1196).

The *systemic actions* of cobra venom were investigated by Cushny and Yagi, 1916. It is strongly hemolytic. Frogs showed mainly a slow curare action. This was also the cause of death in mammals. Superlethal doses also act directly on all forms of muscle, producing first stimulation, then depression. Autonomic nerves, ganglia and myoneural junctions were not affected; nor was there any direct action on the central nervous system. Gautrelet *et al.*, 1934, observed fall of *blood pressure*, chiefly by direct action on the capillaries, increasing their permeability. *Excised intestines* responded to small doses by hypertonus, to large doses by relaxation. Cobra venom *hemolysis* is inhibited by normal mammalian serum, accelerated by inactivated horse serum.

Rattlesnake venom is hemolytic and lowers blood pressure similarly to histamine. It was studied by Essex and Markowitz, 1930. It is not toxic to rattlesnakes. The serum of these snakes, however, is not antitoxic. It, as also the bile, has only a low toxicity (Walker and Marshall, 1915).

Moccasin venom produces intravascular clotting, probably by liberating thrombokinase from the vascular endothelium. It causes clotting when added to oxalated, citrated or hemophilic blood *in vitro*. Injection of a diluted solution has been tried in purpura and other hemorrhagic conditions, but its indications and limitations have not been sufficiently studied. It often causes considerable local reaction (report, Council on Pharmacy and Chemistry, 1940, J.A.M.A., *114:* 2218).

Copperhead venom renders the blood incoagulable and produces a curare effect, with paralysis of respiration.

Scorpion stings, by Centruroides sculpturatus and gertschi, are common in the southwest United States. The poison acts on the nervous system, central, peripheral and autonomic, and is also hemolytic. The effects are more pronounced in children; stings are almost invariably fatal in infants younger than a year, unless they are treated at once. They are dangerous to older children, and a serious inconvenience to adults. The *symptoms in children* consist in pain and extreme restlessness; spastic muscles of the abdomen, arms and legs; quickened heart;

considerable fever; cyanosis; asthmatic, wheezing respiration. Death occurs apparently by exhaustion. In nonfatal cases the symptoms subside within twelve hours. De Magalhaes, 1939, found cavities in the medulla oblongata of fatal cases. *In adults*, the symptoms are similar but less severe. The site of the bite is usually numb. *Rats* die promptly with convulsions (H. E. Essex, 1945). Injection of extracts into anesthetized cats produces fibrillary and clonic contractions of skeletal muscles; hyperpnea, then respiratory paralysis; vasoconstriction; increased salivation, dilated pupils, piloerection. The muscular action is largely peripheral; relatively weak and slow stimulation produces tetanus; small doses antagonize curare, higher doses have a curare action (Del Pozo and Anguiano, 1946). *Treatment* consists in specific antiserum, which has given encouraging results. Barbiturates and bromides give symptomatic relief. Morphine is dangerous and not very effective (M. L. Kent and Stanke, 1939).

The stings of *European scorpions* produce chiefly local irritation (Flury, 1922).

Poisonous Spiders.—The bites of several species may produce local irritation, usually serious. The venom of the *black widow spider*, Latrodectus mactans, however, produces serious results, with violent systemic and local effects, but is rarely fatal for man. It contains a nonhemolytic neurotoxin.

The systemic symptoms may simulate acute abdominal disease, with increased pulse rate, rise of blood pressure, abdominal rigidity, and painful cramps in the leg muscles. Treatment is symptomatic, and includes morphine and barbiturates. Recovery confers complete immunity to the systemic actions, but increased susceptibility to the local effects. An effective antiserum has been prepared (Gajardo-Tobar and Vildosola, 1944).

Bee venom owes its action to a nitrogen-free cyclic acid anhydride somewhat related to cantharidin (Fury, 1929). It is a potent endothelial poison, and produces violent local pain, severe fall of blood pressure on intravenous injection, marked stimulation of smooth muscle, paralysis of perfused hearts, and hemolysis (Essex *et al.*, 1930). Death may occur by low blood pressure or arrest of respiration, preceded by paralysis and convulsions. In rabbits, it causes leukopenia and generally decrease of erythrocytes. Stings of five bees are fatal to mice, twenty to guinea pigs (Derevici and Derevici, 1939). The susceptibility varies with individuals and may be increased or diminished artificially. With sublethal doses, the blood pressure recovers and is then resistant to further injections (tachyhylaxis). It is rendered nontoxic by sulfhydryl compounds, such as reduced glutathione (Brit. Med. J., 1940, 623).

Bee venom has been used therapeutically against arthritis, neuritis and trachoma, but its value is doubtful (review, J. L. Hollander, 1941).

Mosquito venom possibly resembles that of bees (review, J.A.M.A., 1942, *120*:726).

Mussel Poison.—Eating of Mystilus californicus may produce toxic effects, with death in six to ten hours by failure of the respiration and heart (M. Prinzmetal *et al.*, 1932). The toxicity varies; it may be entirely absent and then appear in a few days. It is not bacterial (E. Meyer *et al.*, 1928).

Ascaris Poison.—Ascaris and other intestinal parasites yield a propeptone that is extremely toxic. The symptoms resemble those of peptone injection. Local application to the conjunctiva produces irritation. This substance is not hemolytic (Torai and Hajime, 1917). Ascaris lumbricoides also contains a *hemolytic* substance. This is confined to the digestive tract of the worms and is probably used for the digestion of blood by the parasites. Its action is inhibited by serum, so that it is probably not concerned in anemia.

◆

ANTERIOR PITUITARY HORMONES

The anterior and the intermediate portions of the pituitary gland lack the acute actions of the posterior lobe (Burn and Dale, 1922). The anterior, however, performs vastly more important functions in life. It secretes a considerable number of important hormones which act upon other glands of internal secretion, whose hormones in turn react upon the anterior pituitary activity, so that this small gland serves as a regulating center of endocrine activity. It exists fully differentiated in the most primitive vertebrates, but not below these (review, A. Gorbman). Its *excision* is not fatal, but leads to marked changes, including arrest of growth (dwarfism), and retention of juvenile characteristics; atrophy of the gonads (sexual infantilism); involution of the thyroid and suprarenal and other endocrine glands, decreased metabolic rate, deposition of fat in depots, hypersensitivity to insulin; and some other effects. Administration of the gland or extracts corrects all the derangements of its excision. With normal young animals it leads to excessive growth, precocious sexual development and thyroid hypertrophy (reviews, P. E. Smith, 1935). The several actions of the anterior pituitary are produced by distinct *hormones*. Six, the lactogenic, adrenotropic, growth, luteinizing, thyrotropic and follicle-stimulating, have been isolated in considerable purity. They are proteins (review, A. White, 1946). The gonadotropic and lactogenic hormones will be discussed under sex hormones. Commercial preparations are relatively crude. There is no critical evidence that they have clinical value (S. C. Freed, 1941).

Growth Hormone.—Probably all dwarfism is due to deficient anterior pituitary functionation. With cretins this may perhaps be depressed by ineffective hyperfunctionation of the thyroid gland. Resumption of growth of dwarfed children has sometimes followed the clinical administration of effective anterior pituitary preparations (Engelbach and Schaefer, 1934), but these are difficult to supply. The growth hormone is naturally less important in adults; but as this hormone is present in the adult gland, continued function may perhaps be assumed for the normal tissue replacement. *Overproduction* of the growth hormone is responsible for gigantism, a symmetrical overgrowth in youth, and for acromegaly, an asymmetrical overgrowth in adult life. These have been confirmed experimentally, acromegaly in dogs (not in rabbits and rats), and gigantism in rats. The hormone appears to be found in the eosinophile cells of the gland. Its action differs from that of other hormones and vitamins it involves: chiefly stimulation of the epiphyseal cartilages, but the soft tissues and viscera are also affected (P. E. Smith, 1940). The growth is attributable to increased formation and diminished catabolism of protein (C. N. H. Long, 1942). In animals that have ceased to grow it may accelerate skeletal aging and result in osteoporotic changes (O. Riddle, 1935).

Excision of the anterior pituitary lobe of young animals produces immediate stasis of growth, fixing the infantile proportions and structual peculiarities, such as milk dentition, lanugo hair, open epiphyseal cartilages. Aging of dwarfs follows peculiar patterns; for instance, shrinkage of epiphyseal cartilage. When the pituitary growth hormone is injected, growth resumes and reaches normal proportions or more. Ablated animals are far more sensitive to the growth hormone; but its effects can also be shown on normal *rats and mice*, for these rodents have a latent power of growth and are almost unique among mammals, becuase their epiphyses remain cartilaginous. Administration of pituitary enables them to grow to double the normal size; but the effect is limited to a certain maximal rate which is never greater than the most rapid postnatal growth rate, and this is not increased by increasing the dosage; after a year or a year and a half it becomes progressively slowed. When the administration is stopped, there is an abrupt fall of weight, but the bony frame remains enlarged (Evans and Long, 1921; Evans, 1933).

Tumor Growth.—It is reported that extirpation or irradiation of the hypophysis slows the rate of growth of experimental tumors, and that this is accelerated by administering the gland to such animals (Hayashi, 1930; F. Bischoff, 1935).

The **thyrotropic hormone** (thyrotropin) is essential for the normal development and function of the thyroid gland. *Deficiency* produces thyroid atrophy and lowered basal metabolism, which are promptly relieved by anterior pituitary administration; and *excess* results promptly in thyroid hypertrophy and the phenomena of hyperthyroidism: increased basal metabolism, increased heart rate, exophthalmus, increased iodine content of the blood and decrease in the gland; and also hastened metamorphosis of tadpoles.

Guinea pigs and rabbits are highly susceptible, rats very little. The thyrotropic hormone may be assayed by the histologic changes it produecs in the thyroid gland (J. G. Heyl and Laqueur, 1935), especially by the increased mitoses revealed with colchicine (P. Bastenie, 1940). Deficiency symptoms are prevented in rats by leaving 10 per cent of the gland tissue (25 per cent in monkeys), although there is little or no regeneration (P. E. Smith, 1940). It induces hyperplasia of thyroid tissue even *in vitro* (Eitel, Krebs and Loeser, 1933). The thyrosecretory and thyroplastic responses may be due to different hormones (Heyl, 1934). The hyperthyroid phenomena do not occur if the thyroid gland has been removed, so that the pituitary does not produce them directly, but by stimulation of the thyroid gland, for which the anterior pituitary hormone is indeed the most effective, and perhaps the only effective stimulus. The toxicosis develops more rapidly than by direct administration of thyroxin (E. Schneider and Widmann, 1932). Iodide administration diminishes the hyperthyroid symptoms of guinea pigs treated with thyrotropic extract (Friedgood, 1936), without interfering with the hyperplasia (E. M. Anderson and Evans, 1937). It is quite possible that cretinism and myxedema are due primarily to pituitary deficiency—they are relieved by anterior pituitary hormone as well as by thyroxin—and that Basedow's disease is due to pituitary hypersecretion. Conversely, the thyroid deficiency produces pituitary hypertrophy, perhaps because this produces more thyrotropic hormone to spur the thyroid to compensation. The thyroid involution which follows prolonged thyroid administration is presumably due to diminished production of thyrotropic hormone. Thyrotropic hormone is increased in the blood of patients with hypothyroidism (Bodart and Fellinger, 1936); contradictory results have been reported for hyperthyroidism. If injections of thyrotropic hormone into normal animals are continued for some weeks, they become ineffective and the blood of these animals contains inhibitory substances, whose injection into normal animals renders these also refractory to the thyrotropic hormone. Similar *antihormones* are formed by and to the parathyrotropic hormone and to the gonadotropic hormone of pregnancy urine, but not to thyroxin or insulin (review, D. L. Thomson, Collip and Selye, 1941).

Diabetogenic (Hyperglycemic) Hormone.—This is antagonistic to insulin and decreases the hypoglycemic response to insulin injection. Hyperactivity of the pituitary may be a factor in diabetes. Excision of the anterior pituitary impairs the normal mechanism for regulating the blood sugar level. The nature of the interrelation is not clear (reviews, J. A. Russell, 1938; B. A. Houssay, 1942).

Injection of anterior pituitary extracts into normal dogs produces hyperglycemia (Evans, 1935; Collip, 1934), acting probably on the liver to cause glyconeogenesis and glycogenolysis. It is also ketogenic.

Deficiency, as by excision of the anterior pituitary, greatly increases the response to insulin and prevents or greatly diminishes the hyperglycemia and acidosis of total pancreatectomy (Houssay and associates, 1931 to 1933), although dogs with the double operation become cachectic and die after six to nine months. Their blood sugar level is unstable; it rises greatly after feeding, but is less responsive to epinephrine. Injection of small amounts of anterior pituitary provokes a marked rise of blood sugar, glycosuria and ketonuria. The neutralization is not due to inactivation of the hormones by each other, but to algebraic summation of their effects, which may have quite different points of attack (review, J. A. Russell, 1938).

Dogs with only the pituitary removed (and with intact pancreas) also show instability of the blood sugar level. This is normal if they are well fed, but falls easily to a fatal level on fasting. They are also hypersensitive to insulin. They can be restored by anterior pituitary injection after a considerable latent period. The blood sugar raising principle may be isolated from normal human urine. (*Adiposity*, which often follows removal of the hypophysis, is not due to this, but to injury of the tuber cinereum.)

Ketogenic Hormone.—Injection of anterior pituitary greatly increases the ketone content of the blood, especially the beta oxybutyric acid (F. Hoffmann and Anselmino, 1931), and the excretion of acetone substances (H. Burn and Ling, 1928 to 1930). The ketogenic hormone appears to be distinct from the hyperglycemic hormone. It may also be present in urine (C. Funk, 1933).

Adrenotropic Hormone.—Excision of the anterior pituitary is followed by marked atrophy of the suprarenal cortex (P. E. Smith, 1930). This may be prevented by the injection of hypophyseal extracts (Evans and associates, 1932). The hormone can be separated from the thyrotropic (Collip, Anderson and Thomson, 1933). The suprarenal medulla is not affected.

Parathyrotropic Hormone.—The evidence for this is not altogether satisfactory (Collip, 1940).

PINEAL GLAND

This is a vestigial remnant of a primitive dorsal eye, but presents some evidence of glandular structure, with sympathetic innervation. It begins to involute early between the seventh year and puberty, but its degeneration is never complete. The literature on the pineal gland abounds in apparently contradictory results (an extensive bibliography is given by Rowntree, Clark and Steinberg, 1936). The phenomena seem to be confined to the prepubertal years, *i. e.*, before the gland has undergone involution. *Neoplasms* of the pineal gland are said to be often associated with precocious physical, mental and sexual development and general overgrowth of the body. Only a few cases are on record, and the reliability of the connection is not established. *Extirpation experiments* have not yielded conclusive results. The early effects are inseparable from traumatism. There are no late changes in adults; in young animals, ablation is said to lead to precocious development (Sarteschi, Foa), but the effects, at best, are not striking.

The gland contains a moderate amount of estrogenic hormone, but it is questionable whether this has any physiologic importance (Silberstein and Engel, 1933; Saphir, 1934). *Intravenous injection* of extracts has no pronounced action on the circulation (Dixon and Halliburton, 1909). It is also practically inactive on excised heart and uterine or intestinal muscle (Fenger, 1916). Ott and Scott, 1912, claimed that it increases the milk secretion in goats. This needs to be confirmed.

Continued Oral or Hypodermic Administration.—Hastened growth and development of young animals and early adolescence have been reported, with the end result of dwarfism associated with sexual precocity (Dana and Berkeley; McCord, 1913; Rowntree *et al.*, 1936); but Sisson and Finney, 1920, failed to secure any effects, at any period. Dana and Berkeley administered dried pineal (3 to 6 mg., $\frac{1}{20}$ to $\frac{1}{10}$ grain, three times daily) in backward young children (to twelve or fifteen years). It had no effect on growth, but they claimed improvement of the mental development. Feeding *tadpoles* with pineal hastens *growth and differentiation*. There is also a constituent (purified by D. Beall, Shapiro and Zwarenstein, 1937) which contracts the melanophores under the skin, thus rendering the color much lighter (McCord and Allen, 1917). *Paramecia* fed with pineal divide twice as rapidly as controls (McCord, 1917). Pineal extracts increase the pulsation frequency of the contractile vacuole, as do also epinephrine and pituitary solution (Feather, 1919).

THYMUS GLAND

The development and involution of this gland are interrelated with the functional activity of the thyroid and of the gonads (Marine, 1924), but the nature of the relation is not clear. *Daily injections of thymus extract into rats* hasten adolescence and increase the growth of the offspring during the period of immaturity. These effects become much more marked if the administration is continued through successive generations. The precocious rats show considerable increase of plasma calcium (11.4 to 13.3 mg. per cent) and inorganic phosphorus (4 to 7.4 mg. per cent) (review, Rowntree, 1935). A diet deficient in choline produces rapid involution of the thymus in rats, and this regenerates when choline is added (Christensen and Griffith, 1942). The thymus is pathologic in many patients with myasthenia gravis, and its excision gives good results in some cases (M. Nellen, 1943). Thymus administration has been tried, but with doubtful results, in Graves' disease, rickets, tuberculosis, hemophilia, infantile atrophy and marasmus. Feeding with thymus hastens growth and retards metamorphosis of *tadpoles* (Gudernatsch), but only as does any other food (Swingle, 1917; Uhlenhuth, 1917). Thymus produces convulsions when fed to *salamander larvae* that are devoid of parathyroid (Uhlenhuth, 1918).

SEX HORMONES

Sexual activity is regulated by a number of hormones which circulate in the blood. The ovaries and testes remain dormant unless they are stimulated by the gonadotropic hormones which originate in the anterior pituitary gland and during pregnancy in the chorionic tissue. The sex glands themselves produce three series of hormones, estrogenic, androgenic and progestational. Several of these have been isolated and their chemical structure identified, and some have been synthesized. They are steroids, relatively simple phenanthrene derivatives, with a five-membered ring attached to one end of the molecule. They are probably formed by degradation of cholesterol, although this has not been proved (review, F. C. Koch, 1937). They are closely related to each other, to the sterols, to vitamin D, to the group of carcinogenic substances and to the bile acids, digitaloid glucosides and morphine. They are also produced by other tissues (notably the chorion) and by plants. The sex hormones formed by the male and female gonads are closely related, and both are found in the blood and urine of both sexes, so that the female blood also contains androgenic hormone, and the male blood contains estrogenic hormone, but in different proportions.

In childhood, small amounts of anterior pituitary gonadotropic hormone keep up a limited output of estrogenic and androgenic hormones which bring about the normal gradual development of the genital apparatus. At *puberty* the output of the gonadotropic hormone increases with corresponding activation of the sex glands and increased output of estrogen and androgen, respectively, which results in the rapid development of the secondary sexual characteristics. At *sex maturity,* the female sexual cycles appear and are reflected in the hormone concentration of the urine (reviews: R. T. Frank, 1935; P. E. Smith, 1935). The estrogenic substances themselves do not stimulate ovarian activity; on the contrary, they tend to inhibit the production of anterior pituitary hormone and thereby tend to inhibit ovarian functionation, but this requires rather large doses, and prolonged administration is necessary for it to become notable. *Ovulation* itself apparently is not controlled by any special hormone, but by the concurrent actions of the follicle-stimulating and luteinizing hormones at the correct stage of follicular development. At the *menopause,* when the sexual cycles cease, the hormone level varies; some women show permanent increase of gonadotropic hormone, perhaps by stimulation of the anterior pituitary through ovarian deficiency.

Therapeutic Uses.—The oral administration of fresh or dried ovary, in substance, or corpus luteum against the disturbances of menopause, which had a vogue for a time, is quite ineffective even in animals (Novak, 1922; E. Allen and Doisy, 1922), although it may act powerfully on the imagination.

The pure principles, when properly administered, produce definite effects and have somewhat restricted therapeutic uses. S. C. Freed, 1941, lists the endocrine preparations available commercially, and their trade names.

Administration.—The absorption of the steroid hormones from the gastro-intestinal tract is relatively poor, and some are destroyed in the liver. Bile plays no important role in their absorption (H. Selye, 1943). Sublingual administration gives rather better absorption, but is still wasteful and uncertain (G. W. Corner, 1944). They should be introduced parenterally by intramuscular injection of oil solutions or by implantation of the crystals. The latter prolongs the actions. Nonsteroid hormones are quite effective by mouth.

Subcutaneous implantation of sterones.—Loose crystals are more effective than compressed pellets (U. J. Salmon *et al.*, 1941). The surface of the latter becomes infiltrated with protein derivatives that retard absorption (S. J. Folley, 1942). The time required for 90 per cent absorption of pellets in rats is about eight weeks for hexestrol; twenty-one weeks for diethylstilbestrol dipropionate; thirty-one weeks for testosterone dipropionate (T. R. Forbes, 1943). When incorporated in melted cholesterol, the absorption is much slower and more uniform (Shimkin and White, 1941).

Menstruation depends on cyclic changes in the balance of the estrogenic and progestational hormones, determined chiefly by the anterior pituitary gonadotropin. Estrogen increases progressively in the intermenstrual period and leads to hyperplasia and hyperemia of the endometrium. When the follicle ruptures and the ovum is discharged, the corpus luteum produces progesterone and the estrogen concentration drops and its influence is modified (E. Shorr, 1940), so that the hyperplasia is suddenly arrested, with partial destruction of the endometrium and consequent bleeding. The progesterone prepares the mucosa for the implantation of the ovum (review, Bartelmez, 1937).

Menotoxin.—Normal human menstrual discharges are highly toxic when injected into rats and rabbits, producing focal hemorrhages and necroses of the adrenal cortex and other organs. The toxicity varies with the amount of endometrial debris. It is due to a euglobulin, presumably a product of autolysis. It is highly antigenic for rabbits, producing a potent protective serum (O. W. Smith and Smith, 1944).

During the first two days of menstruation, various cutaneous glands secrete increased amounts of unidentified substances which are toxic to plants, causing wilting of cut flowers (B. Schick, 1920) and inhibiting growth of lupine seedlings (Macht and Lubin, 1924). The nature and origin of these substances are not known. There is no evidence that they are formed in the uterus.

Hormonal Control of Pregnancy.—The rupture of the ovarian follicle decreases the output of estrogen, and the formation of the corpus luteum increases the output of progesterone, which arrests menstruation and depresses uterine irritability. Toward term, the estrogenic hormones again obtain the upper hand, stimulate uterine contractions and prepare the growth of the duct system of the mammary gland.

The regulation of these hormones is rather obscure. The corpus luteum is essential to the implantation and retention of the fertilized ovum, and its destruction terminates pregnancy. The follicular estrogen production is controlled by the gonadotropic hormones from the anterior pituitary gland and placenta: The placenta is rich in estrogen and still more in progesterone. Estrogenic hormones can apparently be formed in the placenta, for they increase in early pregnancy, even after ovariotomy (in human subjects).

Placental extracts stimulate uterine contractions, and when combined with pituitary extracts, *premature labor* is induced (Ludwig and Lenz, 1923). Extracts of the mammary gland likewise stimulate the uterus (Ott and Scott, 1909). They do not increase the milk flow, at least in the human (Schaeffer and Mackenzie, 1910).

The *natural continuation and termination of pregnancy* is conditioned by the interplay and balance of the mutual antagonism between progesterone and the estrogenic hormone. In rats, guinea pigs and rabbits, pregnancy can be readily interrupted, especially at its early stage and toward term, by the injection of estrogenic hormones, and prolonged by the injection of progesterone (D'Amour and Gustafson, 1933). In unanesthetized rabbits (S. R. M. Reynolds and Firor) the pregnant uterus is refractory to motor stimulation by theelin to the twenty-sixth day, but on the twenty-seventh day this induces abortion. In human pregnancy the injection of theelin has but little effect and is unreliable for terminating pregnancy, even when large doses are administered with pitocin toward term (A. L. Robinson *et al.*, 1933). This is not surprising, as pointed out by Edgar Allen, 1935, in view of the large amounts of estrogenic substance normally present in pregnant women (in contrast to the experimental animals), so that the percentile concentration would be increased relatively little, even by large doses.

The hormonal content of pregnancy urine is high for all sex hormones, but the proportions undergo characteristic changes as pregnancy progresses. The *gonadotropic hormone*, which is the object of the Aschheim-Zondek test, increases promptly, and its effects (ovarian and testicular changes in infantile mice and rats; ovarian changes in mature rabbits) are apparent within a few days after conception, so that the test is decisively positive at the first missed period. It reaches its maximum around the fourth or fifth month of pregnancy and disappears promptly at parturition, within three days, but not as abruptly as the estrogenic hormone. Its source is partly from the anterior pituitary and partly from the placenta, especially the chorion (Hart and Cole, 1934).

The *estrogenic hormone* increases progressively during pregnancy and is especially abundant in the latter half, so that it is more satisfactory for diagnosing the late, rather than the early, stages. It lasts until birth and is concerned in the increased motor activity of the uterus that terminates with parturition. Its source is chiefly in the placenta, and it diminishes rapidly at birth.

Progesterone is more abundant in early pregnancy.

Lactation Hormones.—The growth development of the duct system during pregnancy is caused by the estrogenic hormones. Stilbene, androgenic hormones and desoxycorticosterone, and indirectly, the gonadotropic hormones have the same effects, and all produce the same changes in nonpregnant and in castrated animals; they generally fail, however, after excision of the hypophysis; but mammary growth can be induced in hypophysectomized male mice if both estrogen and prolactin are administered (W. U. Gardner and White, 1941). The development of the secreting alveoli is caused mainly by progesterone; and the actual milk secretion is initiated and maintained by a special anterior pituitary hormone, *prolactin* (review, O. Riddle, 1940).

Lactation is therefore promptly terminated by hypophysectomy. Excess of estrogenic hormones tends to inhibit lactation, which may be a reason why milk secretion is deferred until the end of pregnancy. Copious lactation can be initiated only when a well developed mammary gland is subjected to a high lactogenic content of the anterior pituitary. The latter is low during pregnancy, but increases by two to four times immediately post partum (Meites and Turner, 1942). Neither progesterone nor the fetus plays any part in the lactating mechanism (reviews: Selye *et al.*, 1930; Evans, 1935). After the milk secretion is established, its maintenance depends on the reflexes from the act of suckling (Selye, 1934; review, W. E. Petersen, 1944).

The composition of the milk changes but little with its quantity, nor does the milk sugar level vary with the blood sugar in diabetes (E. Tolstoi, 1935).

The *duckbill* presents the simplest mammary gland, as a large number of structures resembling sweat glands, each opening directly through the skin. The *cow's udder* is a system of collecting ducts opening into a cistern for each quarter (W. E. Petersen, 1942).

Prolactin, the lactogenic hormone of the anterior pituitary, has been isolated as a crystallized protein with homogeneous physical properties (A. White *et al.*, 1942). It is not so potent as the crude extracts which probably stimulate the body generally (Meites and Turner, 1942). Prolactin may be assayed on guinea pigs or by the proliferation of crop glands in pigeons (O. Riddle, 1935), the desquamated epithelium furnishing the "pigeon milk" (Dabrowska, 1932). The results are not parallel for different hypophyseal preparations (W. R. Lyons, 1941), and the pigeon method is generally used (Meites *et al.*, 1941). The crop glands respond to local application (Lyons and Page, 1935). In mammals pretreated with estrone and progesterone, the mammary cell changes characteristic of lactation can be induced by injecting lactogenic hormone into the mammary duct (W. R. Lyons, 1942). Lactogenic hormone maintains the functions of the corpus luteum in rats (Evans *et al.*). It has no other significant effects on the gonads or other tissue (R. O. Green *et al.*, 1942).

Administration of prolactin extract to stimulate deficient *lactation* has been tried clinically with fair but variable success (review, W. E. Petersen, 1944). S. G. Wilson, 1943, reports that 100 international units, twice daily, double the output of milk in the first five postpartum days. Injection of *anterior pituitary extract* into cows results in considerable temporary increase of milk (S. J. Folley, 1944).

Estrogens, including ethylstibestrols, increase the growth of the duct system, with slight lobular proliferation. Males require larger doses than do females (W. E. Petersen, 1944). They supplement progesterone to produce alveolar growth (C. W. Turner and Frank, 1932). Excessive doses cause cystic changes in the main duct of rabbits (W. R. Lyons and McGinty, 1941). Meites and Turner, 1942, showed that estrogens, diethylstilbestrol and *testosterone* increase the output of lactogenic hormone, and small doses of estrogens may increase milk production (Folley and Malpress, 1944). Large doses inhibit milk secretion and engorgement of the breasts, if administered early in the puerperium before lactation is established, but they are not effective later. This is used clinically (review, W. E. Petersen, 1944). *Adrenal ablation* inhibits lactation completely. This is prevented by administering cortical extract (J. L. Carr, 1931), but not by desoxycorticosterone (R. Gaunt, 1941). *Thyroxin,* 0.2 mg. per Kg. per day hypodermically, increases the milk volume of cows 28 per cent, the fat output by 50 per cent (S. J. Folley, 1944).

GONADOTROPIC HORMONES

These act by steering the production of the direct sex hormones in the ovaries and testicles, and perhaps in other situations especially at puberty, and in the female during the cycles of menstruation and pregnancy. They circulate in the blood and are excreted by the urine, where they may be used for the diagnosis of pregnancy, and from which active extracts may be obtained for therapeutic use. They are formed by the anterior pituitary gland and by the chorionic villi of the placenta and of chorionic tumors, and perhaps by other tissues. They differ somewhat according to the origin; considerable confusion arose before the dual origin was understood. The *anterior pituitary gonadotropic hormone* is responsible for the actions of the blood and urine of normal men and women, and of women after menopause, natural or artificial. The *chorionic gonadotropic hormone* occurs in the blood in the presence of living chorionic tissue, normal (in pregnancy) or pathological. Human chorionic gonadotropin is excreted by the urine; but little of that of mares' serum (review, E. T. Engle and Levin, 1941). The properties of the latter resemble those of the anterior pituitary more than of the chorionic.

Anterior pituitary gonadotropin appears to contain two distinct active principles: (1) *The folliculotropic hormone* (*"Prolan A"*) acts chiefly on the germ cells in *females.* It stimulates the normal growth and maturation of the graafian follicles and the production of estrone, probably by the cells of the theca interna, and thus leads to estrus and ovulation. *In males,* it stimulates the seminiferous tubules, and induces spermatogenesis. (2) The *luteinizing hormone* (*"Prolan B"*) acts on the connective tissue derivatives. *In females* this causes luteinization of the follicles, ovulation, the progressive development of the corpus luteum and the production of progesterone. *In males* it stimulates the interstitial cells of the testes and the formation of androgenic hormone. The existence of two distinct pituitary gonadotropins has been disputed, and the different effects attributed to dosage, more being required for luteinization.

Luteinizing hormones have been reported from fish and birds which do not form corporea lutea (review, Gorbman).

Excision of the anterior pituitary arrests the genital development in immature animals. In adults it produces some regression and atrophy of the reproductive system (Crowe, Cushing and Homans, 1910). *Administration of anterior pituitary extracts* promptly revives the development, more effectively in the female. Injection of anterior pituitary extracts or implantation of the gland into normal immature rats or mice stimulates the development of the ovaries, with other signs of precocious sexual maturity, within four days (Zondek and Aschheim, 1926; P. E. Smith, 1926). The gonadotropic hormones are generally believed to be formed by the basophilic cells of the anterior pituitary.

Long-continued injections of pituitary gonadotropic extract (over three months) into young puppies produce the phenomena of the clinical syndrome of pituitary basophilism: adiposity plethora; checked growth of the body, teeth and hair; subnormal basal metabolism; high serum calcium, low sugar tolerance, massive glycogen storage in the liver (K. W. Thompson and Cushing, 1934).

Relation to Parathyroid and Calcium.—Injection of the anterior pituitary extract produces histologic changes in the parathyroids and rise of serum calcium, attributable to mobilization of estrogenic and thyrotropic hormones (Riddle and Dotti, 1936).

Creatinuria.—Injection of gonadotropic extract increases the output of creatine, the corpus luteum opposing the transformation into creatinine. This accounts for the creatinuria of pregnancy (Schrire and Zwarenstein, 1934).

Chorionic gonadotropin is almost wholly responsible for the gonadotropic action of pregnancy urines. It is prepared commercially from pregnancy urine and from placenta. It is formed in the chorionic cells. It has been called follutein prolan (A and B), antuitrin, antophysin and prehormone. It induces follicular growth and corpus luteum formation in rodents, but not in human or primate ovaries. In these it tends rather to produce degeneration changes, a striking difference from anterior pituitary gonadotropin. It stimulates the interstitial cells of the testicles to the elaboration of androgenic hormone, which induces growth of the accessory sex organs, in man and monkeys as well as lower animals. It has little if any effect on the germinal epithelium. It is formed by the chorionic placental cells, even when growing *in vitro* as tissue cultures, possibly by the Langerhans cells (Gey, Seegar and Hellman, 1938). It is a glycoprotein containing 12 per cent of galactose.

The *pregnancy test of Aschheim and Zondek*, and its modifications, involve the rapid growth and rupture of ovarian follicles by the gonadotropic hormone of the pregnancy urine. This has been confirmed in women. If the gonadotropic fraction of the urine of pregnant mares is injected before laparotomy, the follicles mature and rupture and corpus luteum is formed, within twenty-four to thirty-six hours after injection (M. E. Davis and Koff, 1938). Injection into very young female rats results in *masculinization*, similarly to testosterone (Bradbury, 1939).

Therapeutic Uses.—Injections of chorionic gonadotropic extracts are used to secure the descent of the testicles in certain cases of functional cryptorchidism (Shapiro, 1930). It has been used against uterine bleeding, but with questionable results. It has little or no value in ovarian disturbances or other conditions (report, Council on Pharmacy and Chemistry, 1940, J.A.M.A., *114:* 487).

In *cryptorchidism*, gonadotropic treatment is effective in 20 to 50 per cent of the patients, but with most of these the testicles would probably descend spontaneously with the natural increase of testicular hormone at puberty (W. W. Johnson, 1939). The administation of the gonadotropin shows whether the testicles can descend, without waiting for puberty; and if it is ineffective, surgical treatment may be undertaken earlier and with better results.

The treatment is best given between the second and third years, injecting 200 to 500 international rat units hypodermically two or three times a week, for one to two months. If it is not effective by this time, surgery becomes indicated (B. Webster, 1935; W. O. Thompson, Bevan *et al.*, 1937; C. I. Deming, 1937; Zeithaml, 1938). The injections may cause precocious sexual development (increased growth of penis, scrotum and prostate) and should be stopped before this becomes marked (W. O. Thompson and Heckel, 1938).

Chorionic Gonadotropin, N.N.R., *Follutein*, *Korotrin*, is a water-soluble substance obtained from the urine of pregnant women, standardized in international units equal to 0.1 mg. of a standard powder. Marketed in vials of 500 to 10,000 units. Dose in cryptorchidism, 200 to 500 units two or three times a week for not longer than eight weeks.

ESTROGENIC HORMONES

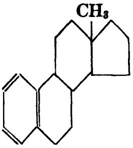
Estrus, the restricted period of mating activity in the females of most mammals, is ushered in by rapid growth changes in the genital tract and the mammary glands, and multiplication and cornification of the vaginal epithelium. These changes may be evoked by the injection of the estrogenic hormone isolated from the follicular fluid, or from pregnancy urine or other sources or prepared synthetically (review, Edgar Allen, 1935).

Historical.—R. T. Frank, 1922, demonstrated estrogenic activity in the fluid of the graafian follicles. E. Allen and Doisy, 1923, confirmed and extended these observations. When Aschheim and Zondek, 1927, demonstrated estrogenic substances in the urine of pregnant women, this furnished a source of supply sufficient for extensive purification, and from this material Doisy, Veler and Thayer, 1929, isolated the crystallized principle which they named *Theelin*, from the Greek adjective theelys, female. Shortly thereafter the same substance was isolated independently by G. F. Marrian, by Butenandt, and by E. Laqueur and associates. The English termed it "*Oestrin*," and Laqueur "*Menformon*." It has also been called "*Folliculin*," which is confusing since it is generally prepared from other sources than ovarian follicles. Theelin is a phenathrene ketone, "ketohydroxy estrin." Two closely related derivatives have also been isolated from pregnancy urines: Theelol or trihydroxy estrin (Doisy and Thayer, 1931), and a hydroxy estrin benzoate (MacCorquedale, Thayer and Doisy, 1935). These differ in their relative actions on immature and on spayed rats (indicating that they do act to some degree on the ovaries).

Nomenclature.—As the designation "Theelin" was not widely accepted, the Council on Pharmacy and Chemistry, on the advice of a committee of workers in this field, adopted in 1936 a system of nomenclature based on the root of "estr" (estrone for theelin, estriol for theelol, and so on), retaining the Doisy names as synonyms.

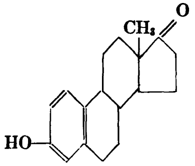
Sources.—In nonpregnant females the estrogenic substances are probably formed in the theca interna of ovarian follicles of all sizes; in pregnancy they come chiefly from the fetal portion of the placenta (review, G. W. Corner, 1938). Estrogens are produced by gonadial tissue even in echinoderms (J. K. Donahue and Jennings, 1937). Theelin is secreted in the maturation of the graafian follicles, and was first demonstrated in the follicular liquid (Doisy and associates, 1934). Its absolute concentration in the ovary is 1:10,000,000, much lower than that of other hormones in their endocrine glands (Doisy). It is ten times more abundant in the urine of pregnant women, which is the usual source of the commercial preparations; but placenta (Allen *et al.*, 1922) and amniotic fluid (Brouha and Simonnet, 1927) also give good yields. It may be prepared from male urine (Laqueur and de Jongh, 1927) and from plants (Dorn *et al.*, 1926). *Theelol* may be prepared from pregnancy urine (Doisy and Thayer, 1931) and from placenta ("emmenin," Collip, Browne and Thompson, 1930).

Chemical Structure.—The estrogenic, androgenic, progestational and adrenal cortical hormones are "*steroids,*" a group name introduced by Callow and Young, 1936, for all substances containing a cyclopentene-phenanthrene carbon skeleton (Marrian, 1939). They include other sterols, bile acids, cardiac glucosides, vitamin D and others. The estrogenic hormones are derived from a nucleus, estratriene, as follows:

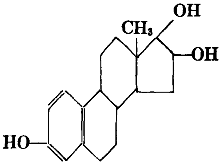


Estratriene

$C_{18}H_{24}$
$\Delta^{1,3,5}$,—estratriene



Estrone
(Theelin)
$C_{18}H_{22}O_2$
3-hydroxy 17-keto
$\Delta^{1,3,5}$,—estratriene



Estriol
(Theelol)
$C_{18}H_{24}O_3$
3, 16, 17-trihydroxy
$\Delta^{1,3,5}$,—estratriene

The structure of the estrogens is related to that of the carcinogenic hydrocarbons of tar, which have some estrogenic action, but are much less potent (J. W. Cook, Dodds and Lawson, 1936). Dodds and Lawson, 1936, also synthesized estrogenic agents without a phenanthrene nucleus. Conversely, the estrogenic hormones are feebly carcinogenic (review, Leo Loeb, 1935).

Assay and Units.—The dosage of the estrogen esters should be expressed in weight, and not as estrogen base, since their potency varies with their absorbability (Council report, 1942, J.A.M.A. *120*:921). The International Unit corresponds to the estrogenic potency of 0.1 gamma of the international standard powder, which is about a third of the amount necessary to induce estrus with vaginal cornification in ovariectomized rats of about 140 Gm. It is about a third of the Doisy unit. A milligram of theelin corresponds to 10,000 international units, when administered in oil. The test can be made more delicate by intravaginal administration, so that it can be applied directly to urine (W. R. Lyons and Templeton, 1936).

Absorption.—Estrone and estriol are soluble in oil and only slightly soluble in water. They are absorbed from the digestive tract as well as from subcutaneous injections, but the steroid estrogens and androgens are to a great extent inactivated in the liver (G. R. Biskind and Mack, 1939), largely by excretion into the bile (Cantarow *et al.*, 1945). They are therefore much less effective by mouth. Diethylstilbestrol is but little attacked by the liver and is therefore better suited for oral administration (M. I. Allen, 1941). Estrogens and androgens are absorbed very well from ointments applied to the intact skin; indeed, the effect of a given quantity is greatest by this channel, because the more gradual absorption maintains it longer in the blood (Zondek, 1935; C. R. Moore *et al.*, 1938). Full therapeutic effects may be obtained clinically by this method (U. Salmon, 1938).

Fate and Excretion.—After intravenous injection, the estrogenic hormones disappear rapidly from the blood (R. T. Frank, Goldberger and Spielman, 1932). With clinical administration, at most 20 per cent is excreted, chiefly by the urine (review, Doisy *et al.*, 1942). They are conjugated with glycuronic acid (Odell and Marrian, 1936). The conjugates are inactive physiologically, but activity may be restored by hydrolysis. Thiamine deficiency interferes with the hepatic destruction of estrone, even when no organic lesions of the liver are apparent (M. S. Biskind and Biskind, 1942). Because of the rapid elimination, the more slowly absorbed esters with fatty acids (benzoate, acetate, propionate) are relatively more efficient.

The **actions of the estrogen** consist fundamentally in stimulation of the anatomical development of the accessory female genital system: the vagina, uterus, uterine tubes (not the ovaries); and in stimulation of the excitability of the uterine muscle. These effects are associated with vasodilatation on the sex organs, demonstrated by Hechter *et al.*, 1941. By the specialized rapid growth promotion, injection of appropriate doses can bring immature female rats or mice with or without ovaries to the sexually mature condition in four or five days; so it is apparently responsible for puberty. As part of this action it induces the special *secondary female sexual characters*, such as the plumage of birds and the sexual swelling and reddening of certain monkeys. In mature females, it *induces estrus;* and as a part of this, the cornification of the *vaginal epithelium*, in a few days, which may be accurately followed by the types of cells in vaginal smears (Stockard and Papanicolau, 1917). The latter occurs also in human subjects. This is utilized for its biological recognition and assay. A slight increase of *basal metabolism* has been described (McClendon *et al.*, 1929; E. Lacqueur *et al.*, 1927); it is denied by others (M. M. Kunde *et al.*, 1931). Its continued administration causes the development of the *mammary duct system*, but extensive alveolar formation requires the anterior pituitary lactogenic hormone. The growth of the mammary ducts is due to a local action, for it is confined to one side by local application (review, W. E. Petersen, 1944). Estrogen does not stimulate the *ovaries* in any way; on the contrary, increase of estrogen tends to inhibit the production of gonadotropic hormone by the anterior pituitary gland, and long-continued administration is said to decrease their size. The *motor excitability of the uterus* is increased and it is sensitized to pitocin (Bourne and Burn, 1928; Scarborough, 1928). S. R. M. Reynolds, 1938, attributed the hyperemia of the uterine tissue and its increased motor excitability in part to liberation of acetylcholine in the uterus. The actions of estrogen and progesterone are partly antagonistic; changes in their equilibrium are largely responsible for the phenomena of the female sexual cycles.

Excessive doses of theelin (at least up to ten times the therapeutic dose) do not appear to produce directly toxic effects, according to most observers (E. Laqueur and de Jongh, 1928; J. A. Morrell *et al.*, 1930), but long-continued injections may induce hyperplastic and then metaplastic changes in the uterus, cervix and breast.

Large doses, at least 70,000 I.U., inhibit the menstrual cycle by inhibiting the gonadotropic secretion of the anterior pituitary, thereby preventing the development of the corpus luteum and the formation of progesterone. Still larger doses, more than 600,000 I.U., may cause glandular cystic hyperplasia of the uterine mucosa. With 6,000,000 I.U. administered during sixty days, functional castration resulted, by preventing the ripening of the follicles. The cervical glands were markedly enlarged and the portio developed a large papillary, but not carcinomatous, erosion. The anterior pituitary reacted with marked increase of eosinophile cells. Other endocrine glands appeared normal (Zondek, 1940). The anterior pituitary also showed histologic indications of hypersecretion on implanting stilbestrol or hexadiene into immature rats (C. L. Foster, 1942). Prolonged administration of theelin with 100,000 to 200,000 rat units in divided doses over two or three months (Mayer, Meranze and Israel, 1935) produced no appreciable change in body weight, basal metabolism, blood pressure, blood count, coagulation or bleeding time. Sometimes there was a secondary delay of menstruation, probably by inhibition of the anterior pituitary. A few showed growth of mammary glands and increased libido.

Relatively large doses in *rabbits* showed no macroscopic changes in the vital organs. The response of the ovaries to huge doses was sometimes stimulant, sometimes degenerative. Very prolonged administration (five to eight months) to female rats has an unfavorable tendency on fertility, gestation and lactation (Wade. 1934).

Carcinogenic Activity.—Several investigators have produced mammary cancer, pituitary hypertrophy, adenomas and carcinoid changes in the vagina and uterus, and sarcomas, all in mice, and cervical growths, possibly precancerous, in monkeys (Geschickter *et al.*, 1934; Witherspoon, 1935; W. U. Gardner *et al.*, 1936; review E. Allen, 1942), raising the question of the possibility of causative connection with human mammary, uterine and prostatic tumors. This enjoins caution in the clinical use, although these experimental effects require doses of estrogen enormously greater than are used clinically (Doisy, 1937). Geist and Salmon, 1941, who made biopsy studies of vaginal and endometrial changes during prolonged administration in a large group of women, found no indication of genital carcinoma even with doses that added to 53 million international units. The very large doses administered by Zondek, 1940, did not result in cancer in these women; but individual susceptibility varies greatly, even in animals.

Intersexuality.—Administration of large amounts of estrogens to pregnant rats results in intersexed or feminized male offspring (R. R. Greene, Burrill and Ivy, 1938). Similarly, androgen administration yields masculinized female offspring (Greene and Ivy, 1937).

Effects of Estrogenic Substances on Males.—Prolonged administration of theelin to *mature male* rats somewhat retards their body growth and decreases the weight of their genitalia, but the reproductive capacity remains normal (Wade, 1934). Beuthner and Fals, 1928, found no change in mature males, with their dosage, but immature males reacted with degenerative changes in the testicles, with recovery on discontinuance. Laqueur, 1932, observed more marked "antimasculine" changes, including impeded development and degeneration of the testicles and atrophy of the secondary characteristics, including the seminal vesicles; but in castrated animals, menformon promoted the development of the seminal vesicles.

Prostatic carcinoma is sometimes strikingly improved by administration of estradiol or diethylstilbestrol, as by castration or irradiation of the testicles. The extension of the tumors is slowed, and the clinical symptoms are relieved, so that life is more comfortable in half of the patients, although no cure has yet been reported (C. L. Deming, 1946). The mechanism is obscure (W. P. Herbst, 1942).

Ovipositor Reaction of Bitterling.—The injection of estrogen into this fish (Rhodeus amarus), or its addition to the water in which the fish is kept, produces marked enlargement of the ovipositor (Fleischmann and Kann, 1932). The reaction also follows administration of the urine of pregnant women (A. E. Kanter *et al.*, 1934), and of adult males. The latter is probably due to corticosterone of the adrenal cortex, which gives the same reaction. It is not produced by anterior pituitary extract (Fleischmann and Kann, 1938).

Skeleton and Blood Calcium Level.—Injection of estrogenic hormones or diethylstilbestrol into birds raises the level of serum calcium and accelerates the formation of endosteal bone. The latter is probably due to stimulation of the osteoblasts, not to the calcium increase. There is also a large rise in blood lipid phosphorus and increased excretion of phosphate released from the bones (W. U. Gardner and Pfeiffer, 1945). The oviducts also show increased growth (M. R. McDonald, Riddle and Smith, 1945). The breakdown and ossification of growing cartilage is accelerated by estrogens (M. Silberberg and Silberberg, 1939). In mice, estrogens produce hypercalcification of the skeleton, with partial or complete obliteration of the marrow cavity. This is prevented by the simultaneous administration of testosterone (W. W. Gardner and Pfeiffer, 1938).

Lipemia.—Long-continued injections of large doses of estrogenic hormones into roosters greatly increase the fat content of the blood, by the mobilization of tissue fat. Other sterols lack this action. It is not mediated through the anterior pituitary gland and does not occur in mammals (Zondek and Marx, 1939).

Anesthetic Effects of Steroid Hormones.—Intra-abdominal injection of sufficient doses of all steroid hormones and of stilbestrol derivatives produces depression and loss of consciousness, which Selye and Heard interpret as "anesthesia"; but D. B. Farson *et al.*, 1946, who produced analogous effects with intravenous injection of cholesterol suspensions, report that response to pain persists. Daily injection of the steroid hormones rapidly induces tolerance, which extends to the other derivatives. The action is stronger in vertebrates with relatively lower nervous development. Invertebrates are completely resistant (H. Selye and Heard, 1943).

Antagonism to Alcohol Narcosis.—The susceptibility of female rabbits to the acute narcotic effects of alcohol is increased by castration, and decreased by administering estrone, so that a higher blood level of alcohol is necessary (L. Goldberg and Störtebecker, 1943).

Root growth of lupine seedlings is stimulated by estrone, 1:200,000, inhibited by progesterone. Diethylstilbestrol is slightly inhibiting (D. I. Macht, 1946).

The therapeutic use of estrogens in gonorrheal vulvovaginitis of children was suggested by R. M. Lewis, 1933, to render the soft epithelium cornified and more resistant, as is the adult vaginal epithelium. Good results were reported from intramuscular injections of 200 international units, 0.1 mg. of estrone, every second or third day, or vaginal suppositories of 2000 units (Mazer and Schechter, 1939), until the smears are negative. This treatment, however, has been generally abandoned, as further experience has shown that the gonococci are not killed, and the estrogenic effects on the child (engorgement of the breasts, growth of pubic hair; J. J. Reichert *et al.*, 1937) are undesirable, although they usually return to normal promptly on cessation of the injections. Experience with monkeys indicates that the ovaries are not damaged by the treatment (Doisy, 1937, review). It is probably more useful in senile vaginitis. Up to 5 mg. (50,000 I.U.) weekly may be required. Beneficial results have been reported from injections of estrogenic hormones in *atrophic rhinitis* (Mortimer, Wright and Collip, 1937; Blaisdell, 1938); but Soskin and Bernheimer, 1939, attributed the improvement to vasodilatation by increase of acetylcholine.

Treatment of Menopause Symptoms.—Administration of estrogens generally decreases materially the phenomena of natural and surgical menopause and helps substantially to tide over the period of adjustment. The nervousness, fatigue and mental depression, the number and intensity of the vasomotor crises, the "hot flashes" and the decrease of basal metabolic rate are improved within ten days. The vaginal epithelium also returns to the natural menstrual type. When the administration is omitted, all the phenomena recur; but with long-continued administration they become gradually less (Papanicolaou and Shorr, 1936; Mayer and Israel, 1937; Collett *et al.*, 1937; Doisy, 1937, review). The dosage must be adjusted by the results; 250 to 1000 units of estrone or estriol per day generally suffice. Oral administration of either estrone or estriol gives probably as good results with equal dosage as do intramuscular injections, and the effects are more lasting. Large doses sometimes cause considerable uterine bleeding.

The basal metabolic rate of castrated women is disturbed by the administration of estrogenic hormones. Small doses, 500 to 1000 I.U. of estrone, produce a prompt and fairly large increase of the B.M.R.; larger doses, 1000 to

2000 I.U., result in less rise or in fall of B.M.R. (Collett, Reed *et al.*, 1940).

The *electro-encephalogram* in post-menopausal mental patients is not changed by stilbestrol or progesterone (Cress and Greenblatt, 1945).

The *use of estrogens in dysmenorrheas of various kinds* is generally not advisable. They would need to be adapted to the varying balance of estrogen and other sex hormones, which is not feasible (review, Novak, 1934).

Acne and hypertrichosis have been treated with estrogenic substance, but this has not been very successful and should not be used unless there is other evidence of ovarian disturbance (L. M. McCarthy and Hunter, 1937).

Termination of pregnancy may be induced in rats through estrogenic injection, by the stimulation of uterine contractions. Estrone, administered before implantation, caused hyperplasia of the mucosa and fibrosis. If it was given at various stages after implantation, the embryos were killed, without necessarily damaging the uterus (D'Amour and Gustavson, 1934).

Hemophilia.—Estrone has been tried with the assumption that the immunity of women to this condition may be due to the female sex hormone (Grant, 1904; Birch, 1931). The theoretical basis was not sound, since the immunity is supposedly a chromosome characteristic, which would not be affected by hormones. Careful trials on seven hemophilic patients were entirely unsuccessful; nor did the urines of untreated patients show any deficiency in estrogenic hormone (R. B. Stetson and associates, 1934).

L. Loewe and Lenke, 1938, failed to confirm the claim that theelin protects rats against *peripheral gangrene* induced by ergotamine.

Cutaneous administration of estrogenic hormone as ointments has about a seventh of the potency of injections; the absorption is much better from solutions in benzene, ether or alcohol (Zondek, 1938). If the ointment is applied to the breast it acts particularly at this site, but requires doses which also have systemic effects (MacBryde, 1939).

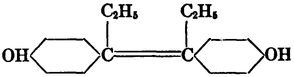
Ethinyl estradiol is effectively absorbed through the skin of rats, when applied as alcoholic solution (C. F. Morgan and Ponzio, 1944).

Preparations.—*Estradiol*, U.S.P.; alpha estradiol; dihydrotheelin; a white, crystalline powder, odorless and tasteless; stable in air; almost insoluble in water, soluble in alcohol and in aqueous solutions of fixed alkalis, sparingly soluble in oils. Average dose, 0.2 mg. *Estradiol Benzoate*, U.S.P.; almost insoluble in water, soluble in alcohol, sparingly soluble in oil. Average dose, 1 mg. intramuscularly, once or twice per week. *Estriol* (*Theelol*), N.N.R.; characters and solubility as for estrone; considerably less potent. Marketed as capsules of 0.06, 0.12 and 0.24 mg. Dose, 0.06 to 0.12 mg. once to four times daily. *Estrone* (*Theelin*), U.S.P., small white, odorless crystals, practically insoluble in water, soluble in alcohol and in oils. One mg. = 10,000 International Units. Marketed in ampuls of oil solutions, 0.1, 0.2 and 1 mg., and suppositories of 0.02 and 0.2 mg. Dose, 0.2 to 1 mg. once or twice a week. *Commercial noncrystalline preparations* from the urine of pregnant women or pregnant mares or placental extracts contain chiefly estrone (S. C. Freed, 1941). Several brands of these *Estrogenic substances* are listed in N.N.R.

DIETHYLSTILBESTROL

Diethylstilbestrol, triphenyl-ethylene and a number of other synthetic substances of relatively simple structure, not containing the phenanthrene ring, produce all the effects of the natural estrogenic substances and are clinically effective for replacement therapy in menopause, to secure cornification of vaginal epithelium (Russ and Collins, 1940), to inhibit lactation, to check obstruction and metastases in prostatic carcinoma (B. G. Clark and Viets, 1943), and for the other uses of estrogenic substances; with the advantage that stilbestrol is effective by mouth as well as by parenteral injection (with a potency ratio of 1:2 to 5). Undesirable side actions, especially nausea, vomiting and headache, occur rather frequently if the absorption is too rapid. They do no permanent damage. The toxicity is probably no greater than with the natural astrogens.

Diethylstilbestrol,



sometimes misnamed *stilbestrol*, was introduced by E. C. Dodds, Goldberg *et al.*, 1938. It is potent by mouth and parenterally, since relatively little is inactivated by the liver (M. J. Allen and Greengard, 1941; B. Zondek *et al.*, 1943). It is about two and a half times more potent than estrone by injection in animals. Clinically it is less active than estradiol benzoate parenterally, but surpasses it by mouth, losing about half of its activity by this method (review, Council on Pharmacy and Chemistry, 1939; J.A.M.A., *113*:2312). In ten days following a single oral dose of 10 to 15 mg., 10 to 30 per cent is *excreted* by the urine and feces (von Haam *et al.*, 1940).

Numerous derivatives have been examined for correlation of action and *chemical structure*. The most potent have two rings, at least one benzenic; and two OH groups at opposite poles of the molecule (G. Masson, 1945).

Clinical Effect on Lactation.—Diethylstilbestrol effectively prevents or minimizes breast pain and engorgement, if 15 mg. are administered by mouth, promptly for three to ten days after parturition. Lactation is delayed and decreased, but not permanently suppressed even by very large doses (H. F. Connaly *et al.*, 1940; Abarbanel and Goodfriend, 1940). However, estrogenic hormones are now rarely used for this purpose. Prolonged administration of 5 mg. daily *to males* may produce marked mammary enlargement and diminution of sexual function, without other toxic effects, probably by depressing the pituitary gonadotropic secretion (C. W. Dunn, 1940).

The clinical toxicity is not materially greater than with natural estrogens. Indeed, massive and prolonged administration to pregnant or nonpregnant women does not produce serious toxic effects (K. J. Karnaky, 1945). Ten to 20 per cent of patients have minor untoward symptoms, corresponding closely to those of the nausea of pregnancy, and occurring especially with the larger doses and in women who were much nauseated when pregnant (J. W. Finch, 1942): nausea, vomiting, headache, abdominal distress, anorexia, diarrhea, lassitude, paresthesias, vertigo, thirst, acute psychotic reactions, cutaneous rashes, angioneurotic edema (W. Saphir and Weinglass, 1942). They occur on parenteral as well as oral administration. They are attributable to rapid absorption and individual susceptibility (S. C. Freed, 1941). Patients can usually be quickly desensitized by reducing the doses to 0.1 mg. per day and increasing by 0.1 mg. every five or six days until the therapeutic level is reached (Finch, 1942). Abnormal uterine bleeding is rather frequent when diethylstilbestrol is administered at menopause, and it is advisable to use it only when really needed (E. Novak, 1944).

Large doses (330 mg. by mouth in seven days) do not appear to interfere with the progress of human pregnancy, although they may do so in animals by eliminating the action of the pituitary gonadotropic hormone on the corpus luteum (Zondek and Bromberg, 1942). No tissue, liver or blood damage has been demonstrated clinically, even with prolonged administration (von Haam, Hammel *et al.*, 1940), and with large doses (10 mg. daily) to women who had previously some liver dysfunction (S. C. Freed, Rosenbaum and Soskin, 1940). It appears inadvisable to administer extensive courses to patients with a cancerous family history (Buxton and Engle, 1939).

Toxic Effects on Animals.—Dogs (O. Arnold and Hamperl, 1939), rats and rabbits may show blood and organ changes, cloudy swelling, congestion and necrosis of the kidneys, liver and adrenals. Mice die in ten to sixteen days after administration of 0.1 to 1 mg. per Gm.; rats die in an hour after 1.5 to 5 mg. per Gm. (Krietmair and Sieckmann, 1939). Rats have decreased appetite; nasal, vaginal and intestinal hemorrhages; fatty degeneration of the liver with subsequent necrosis; and other lesions (A. Loeser, 1939). Disturbances of the myelogenic system, with granulocytopenia and anemia, have been reported in dogs (R. Tislowitz, 1939). Intravenous injection of 10 to 20 mg. into dogs produces prompt increase of capillary fragility and purpura. This is cured by alpha tocopherol (F. Skinner *et al.*, 1946).

Secretory exhaustion of the anterior pituitary with cytoplasmic vacuolization has been described for immature rats (C. L. Foster, 1942). No carcinomas were observed after implantation of large doses in rats (C. R. Page *et al.*, 1941). Male mice showed retarded growth, atrophy of the viscera, especially the spleen; decreased spermatogenesis, and mammary cancers (Shimkin and Grady, 1941).

Intramuscular injections for twenty-four days did not induce hypertension in rats (H. C. Hill, 1946).

Diabetes is produced in rats by the administration of the stilbestrols in large doses. The hepatic glycogen is markedly increased (R. S. Teague, 1942), as is also the insulin content of the pancreas in rabbits (M. Griffiths, 1942). It is mediated partly but not altogether through the adrenals and anterior pituitary. It occurs after partial pancreatectomy (D. J. Ingle, 1944).

PREPARATIONS.—**Diethylstilbestrol**, U.S.P., a white, crystalline powder, slightly soluble in water and dilute mineral acids, soluble in dilute alkalis, alcohol and fat solvents. Dosage, 0.2 mg. (1/300 grain), increased to 0.5 to 1 mg. daily by mouth; or similar doses one or more times weekly by intramuscular injection. Administered orally as *Diethylstilbestrol Capsules* and *Tablets*, U.S.P., usually available as 0.1, 0.5 and 1 mg.; intramuscularly as *Diethylstilbestrol Injection*, U.S.P., a sterile solution in oil or other suitable solvent, usually available in ampuls of 0.5 mg. and 1 mg. in 1 cc. *Vaginal suppositories* (0.1 and 0.5 mg.) may be used in vaginal conditions. *Subcutaneous implantation* of a cylindrical pellet of 50 mg. of crystalline diethylstilbestrol yields a constant daily absorption of 0.35 to 0.45 mg. for about a hundred days. Two or three such pellets are implanted for palliation of prostatic carcinoma (Shimkin and Zon, 1943).

Diethylstilbestrol esters are more slowly absorbed, securing the advantage of more prolonged and less intensive action. The *dipalmitate* is superior to the dipropionate in this respect (S. C. Freed *et al.*, 1942). *Monomethyl ether* (*Monomestrol*, N.N.R., *Mestibol*) has also been proposed (Geschickter and Byrnes, 1942).

Hexestrol, dihydro diethylstilbestrol, $(C_6H_4OH)_2$-$(CHC_2H_5)_2$, has the same action as diethylstilbestrol with the doubtful claim of lower incidence of toxic symptoms (Bieren and Compton, 1942).

Benzestrol, N.N.R., *Octofollin*, $(C_6H_4OH)_2.(C.H.C_2H_5)_2$-$(CH.CH_3)$, a dihydromethyldiethylstilbestrol, also has the actions of diethylstilbestrol with the claim of fewer untoward actions (H. K. Roberts *et al.*, 1943; E. W. Blanchard *et al.*, 1943). Dosage, 2 to 5 mg. daily by mouth, as tablets (available as 0.5, 1, 2 and 5 mg.); or an injection (available as 5 mg. in 10 cc.).

Triphenylethylene and **Triphenylchlorethylene** are also estrogenic (J. M. Rolson and Schönberg, 1937; A. E. S. Macpherson and Robertson, 1939).

ANDROGENIC HORMONES

A number of steroids closely related chemically to the estrogenic hormones are masculinizing, inducing growth and development of the genital organs of the male, including the secondary sexual characteristics. They counteract the effects of castration in the male, the atrophy of the seminal vesicles, prostate and penis and the diminished libido. In capons they induce growth of the comb and the characteristic male plumage (review, F. C. Koch, 1937). They circulate in the blood of males, and in lower concentration in that of females, but the human male does not show hormone cycles. Their administration constitutes adequate replacement therapy in true testicular deficiency (eunuchism), but their practical applicability has not been determined. This applies also to their use in cryptorchidism. Their influence on prostatic enlargement is questionable. They have little or no effect on senile or psychic impotence, or as aphrodisiac.

Chemistry.—The most important of the androgenic hormones is *testosterone*, a steroid secreted presumably by the interstitial cells of the testes, now generally prepared synthetically as *testosterone propionate*, since the fatty esters are more slowly absorbed from the site of injection and therefore produce a more continuous action. This is also effective on percutaneous application (report, Council on Pharmacy and Chemistry, 1939, J.A.M.A., *112:* 1949).

The *androgenic hormones of male urine* consist chiefly of *androsterone* and dehydroandrosterone, which have relatively little action on mammalian sex tissues. They are excreted as glycuronides which are much less potent and from which they can be easily liberated by acid hydrolysis (review, F. C. Koch, 1938). The urinary androgenic hormones are probably derived from testosterone, which is not found in the urine. When it is injected, it is excreted chiefly as androsterone (Dorfman *et al.*, 1939). *Dehydro-androsterone* is isomeric with testosterone. The chemical structure of androsterone differs from that of estrone only by the addition of a methyl group. It was isolated as pure crystals from human male urine by Butenandt and Tschorning, 1931, and synthesized from cholesterol by Ruzicka, Goldberg *et al.*, 1934. The androgenic hormones of the urine of women have not been isolated sufficiently pure for identification. *Other androgenic hormones* have been found in abnormal conditions, such as hirsutism, and are perhaps formed in the adrenal cortex. Androgenic actions have been demonstrated in some fifty natural and synthetic substances. *Quantitative differences of androgenic* potency exist in normal and abnormal urines of men and women, but are not so great as might be expected (F. C. Koch, 1938).

Effects on Males.—Administration of the androgenic hormones to castrated males prevents and repairs the castration effects. These hormones are recognized and assayed by increasing the *comb growth* in capons (also in hens), restoring the male *plumage pattern*, and the aggressiveness. The effect on the comb is also secured by local application (0.5 gamma of androsterone daily, S. R. Hall and Dryden, 1939). It is antagonized by the local application or injection of estrogen and progesterone; diethylstilbestrol inhibits only on injection (Mühlbock, 1939). Conversely, testosterone, androsterone and progesterone (but not desoxycorticosterone) inhibit the atrophy of male organs by chronic estriol treatment. This action does not parallel the effect on castrates (Albert and Selye, 1942). The androgenic hormones prolong the life and motility of the *spermatozoa* in the seminal vesicles of castrates. In guinea pigs they cause general *muscular hypertrophy*, especially of the temporal muscles (which are normally more developed in males; Papanicolaou and Falk, 1938). They do not stimulate *spermatogenesis*, but rather diminish it by inhibiting the *gonadotropic* function of the *anterior pituitary gland* (review, P. R. Moore, 1934). Injections of testosterone propionate or acetate produce partial or complete regression of *breast hypertrophy* in males (W. J. Hoffman, 1939). They slowly darken the *color of the skin and hair* in castrated men and ovarectomized women (J. B. Hamilton and Hubert, 1939). They tend to produce *descent of the testicles* in cryptorchidism, but are less effective than the gonadotropin of pregnancy urine; they cause frequent erections, growth of the penis, scrotum and pubic hairs (Zeithaml, 1938); and may damage spermatogenesis (C. R. Moore, 1935; W. O. Thompson and Heckel, 1939). Favorable results in "male climacteric" were reported by A. A. Werner, 1939. Vest and Howard, 1939, claimed good results from implantation of testosterone crystals in hypogonadism.

Prostate.—Androgens increase the prostatic secretory epithelium (E. Z. Burkhart, 1939), and excessive doses produce hyperplasia. Estrogens have the opposite effect. This is the basis of the treatment of prostatic cancer by castration and estrogens. Nearly all patients show improvement, often prolonged (C. Huggins, 1943).

The effects of testosterone and estradiol esters on the *resistance to barbiturates* has been studied in rats by H. G. O. Holck *et al.*, 1942.

Effects on Females.—Moderate doses act like estrogenic hormones, but are much less potent. They accelerate the growth and development of the uterus in immature rabbits and cornify the vaginal epithelium in spayed rats (Deanesley and Parkes, 1937). On the other hand, testosterone acts like weak progesterone in that it inhibits contractions of the uterus and renders it irresponsive to pitocin (Leonard, Lager and Hamilton, 1937); it inhibits the onset of menstruation in monkeys (Hartman, 1937), and causes some progestational proliferation, but much less than progesterone (J. Robson, 1937). It produces development of mammary acini in virgin rats (G. L. Laquer, 1943). It tends to suppress estrus by inhibiting the gonadotropic function of the anterior pituitary gland. The administration of large doses to pregnant rats results in intersexed female offspring; *i.e.*, considerable development of the male sex organs and defects in the female organs (R. R. Greene and Burrill, 1938).

Clinically, testosterone propionate has no effect in doses of 200 mg. per month; but with 500 mg. or more per month, it causes temporary suppression of the menstrual cycle, hypoplasia of the endometrium and evidence of estrogen deficiency in the vaginal epithelium. Recovery ensues if the administration is discontinued. Larger doses produce hoarseness, hirsutism, enlargement of the clitoris, acne and increase of weight; these also regress in almost all cases with cessation of the administration (Geist, Salmon *et al.*, 1940). It has been administered to suppress abnormal uterine bleeding in doses of 400 to 2000 mg. per month (J. P. Greenhill and Freed, 1939). It *inhibits lactation* during early puerperium, without the usual pain and discomfort and without undesirable after-effects (Kurzrock and O'Connell, 1938). Hypodermic injections of 25 mg. daily for two or three days suffice if started with the beginning of lactation (not before nor after this time); 5 to 10 mg. relieve the pain of engorged breasts without diminishing secretion (P. V. Duffy and Corsaro, 1941).

PREPARATIONS.—*Testosterone Propionate*, U.S.P. ("perandren"), is the most effective androgenic hormone available for clinical use (S. C. Freed, 1941). It is prepared from bull testes, or synthetically from cholesterol. It is insoluble in water, soluble in alcohol and in oils. One mg. equals 50 International Capon Units. Dosage, 5 to 50 mg., intramuscularly in oil, twice to six times per week. Priapism indicates excessive dosage. Marketed in ampuls of 5, 10 or 25 mg., as oil solution. *Methyltestosterone*, U.S.P., is more potent for oral or sublingual administration (50 to 100 mg. daily; editorial, J.A.M.A., *117*:622, 1941). It is a white crystalline powder, insoluble in water, sparingly soluble in vegetable oils. *Methyltestosterone Tablets,* U.S.P.; usual sizes, 5 and 10 mg.

PROGESTERONE

This, the characteristic hormone of the corpus luteum, produces the extensive development and the secretory activity of the uterine mucosa which are necessary for the implantation of the ovum. Its suppression by excision of the corpus luteum during early pregnancy prevents nidation of the fertilized ovum; or if already implanted, the pregnancy does not proceed to conclusion. Its injection is effective after ovariectomy in producing the endometrial changes of the premenstrual period in women and monkeys, and the pregnancy changes in rabbits and guinea pigs. Progesterone also quiets the spontaneous movements of the uterus (Reynolds and Allen, 1932) and inhibits the response of the uterus (rabbit's excised) to posterior pituitary stimulation (Knauss, 1933). This is probably essential to the continuation of pregnancy, especially to overcome the estrogen which stimulates the uterine motor activity. Small doses administered intravenously during labor decrease uterine activity, but large doses increase the strength and frequency of the contractions (H. Winzeler, 1944). It activates the growth of the mammary alveolar tissue. Its formation in the ovary begins soon after the discharge of the ovum and continues through the first three months of gestation; after this time it is formed by the placenta. It is not established how far progesterone is concerned in other relations of the corpus luteum to sexual functions.

Therapeutic indications for progesterone are not well established. It has been administered in menstrual disorders, amenorrhea (B. Zondek, 1942), habitual functional abortion and menstrual nasal congestion (Willson-Pepper and Royle, 1939).

Progesterone prevents copper-induced *ovulation* in rabbits (M. H. Friedman, 1941). It has no effect on the emptying time of the *stomach* in normal man (Sleeth and Van Liere, 1940).

Chemical Nature.—The characteristic effects were shown on crude extracts by Hisaw, Meyer and Weichert, 1928. Progesterone was isolated in pure crystalline form independently, about 1934, by W. M. Allen, by Butenandt and by Slotta. These and Corner, who was instrumental in its discovery, all agree upon the title "Progesterone" to displace the older titles of corporin, progestin and luteosterone. It is also a steroid, which differs chemically from androsterone only by the addition of a third methyl and a second ketone oxygen in place of a carboxyl (W. M. Allen and Wintersteiner, 1934). It has been synthesized by Butenandt, starting from stigmasterol, a wax obtained from soy beans and from the "pregnandiol" fraction of pregnancy urines. It occurs in two forms differing by a few degrees in melting point. Both forms produce all the typical progesterone actions (W. M. Allen and Reynolds, 1935).

Progesterone is not *excreted* as such, but as a reduction product, pregnandiol, conjugated with glycuronic acid, which is found in the urine of pregnancy and during the corpus luteum phase of the cycle (Marrian, 1939). It increases the urine output of cats (Selye and Bassett, 1940).

Pure *synthetic progesterone* is commercially available. It is not well absorbed from the digestive tract, and is partly destroyed by the liver (G. Masson and Hoffman, 1945), so that it is not very effective by mouth. It is administered hypodermically, generally in oil solution. *Anhydrohydroxyprogesterone* is effective by mouth.

Progesterone, U.S.P.; practically insoluble in water, sparingly in vegetable oils, soluble in alcohol. Average dose, 5 mg. intramuscularly. *Anhydrohydroxyprogesterone,* U.S.P.; average dose, 10 mg.; *Tablets,* U.S.P.; usual sizes, 5 and 10 mg.

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HORMONES OF THE ADRENAL CORTEX

The adrenal cortex is a distinct organ with endocrine functions, elaborating a group of steroids closely related to the sex hormones in structure and, to some degree, in action. Degeneration of the adrenal cortex results in the clinical syndrome of Addison's disease. Its complete removal, in animals in which this may be accomplished, produces no perceptible symptoms for about a week; then the animals rather suddenly develop anorexia, lethargy, muscular weakness, hemorrhagic gastro-enteritis, shock, anhydremia, hypoglycemia, hypercalcemia, and die in one to three days after the onset of the symptoms.

These effects are prevented or checked by the administration of the adrenocortical hormones.

The *time of survival after excision of both suprarenal glands* varies with different animals. With the best operative technic, dogs usually live longer than a week, many survive for ten to twelve days, a few to fourteen days, but practically none longer. Cats generally live one to two weeks, a few three weeks. Guinea pigs die in about a week. Rats vary, but more than half survive indefinitely, presumably by having accessory "interrenal" tissue in other situations (G. N. Stewart, 1926). The *salt content of the diet* has important effects on the survival time. *Pregnancy* prolongs survival, as does also the administration of *anterior pituitary extract* and *progesterone.* Estrogen shortens life. *Partial adrenal deficiency* has been produced in cats and dogs by subtotal ligation of the blood supply. The animals survive four to six months, with acute phenomena and exacerbations, similar to those of

Addison's disease (Rogoff, 1933). *Addison's disease* is a clinical syndrome accompanying degeneration of the adrenal glands. Aside from progressive melanin pigmentation of the skin and buccal mucosa, its phenomena are subacute manifestations of those described for removal of the adrenals: loss of appetite, muscular asthenia and, toward the end, vomiting, diarrhea, cardiac weakness, fall of blood pressure and various neurologic symptoms. It is markedly subject to occasional spontaneous remissions and exacerbations.

Active Constituents.—Five closely related steroid compounds important to life have been isolated from the adrenal cortex. The most important are corticosterone and desoxycorticosterone, the latter being closest to progesterone. The amorphous fraction is also potent. The sex hormones are present in small amounts; also a thyrotropic hormone, and a considerable amount of ascorbic acid (Györgi, 1929). Epinephrine is absent. *Desoxycorticosterone* is the most potent contituent in maintaining life after excision of the adrenal gland, and in its effects on the electrolyte and water balance; but only minute quantities are present in the adrenals, so that it may not play the most important role.

Removal of the Experimental Deficiency Phenomena by Extracts of Suprarenal Cortex.—G. N. Stewart and Rogoff, 1925, were the first to prove that injection of saline extracts of suprarenal cortex secures the survival of animals after complete removal of both suprarenal glands. They designated the (unisolated) hormone as "*interrenalin.*" F. A. Hartman, 1927, called his saline extract "*cortin.*" J. J. Pfiffner and Swingle, 1929, used organic solvents for the extraction; and further improvements have resulted in considerable purification and concentration (Ehrenstein and Britton, 1937; G. Hunter and Cantor, 1937). The extracts may be standardized by bio-assay and are administered hypodermically. *Commercial extracts* are marketed under several names ("*eschatin,*" and so forth). They are sometimes quite ineffective (Rogoff, 1934).

Oral administration of cortical extracts is probably effective, but requires considerably (six to twelve times) greater doses; but in rats oral administration gives better results (Grollman and Firor, 1936). It is probably not advisable clinically, even to supplement the injections, for unless the medulla is removed from the gland immediately after death, the material is highly toxic and therapeutically ineffective. (A. Grollman and Firor, 1934).

Desoxycorticosterone is the most potent of the isolated constituents for maintaining life after adrenalectomy, but the amorphous fraction is almost equally potent. Corticosterone requires larger amounts.

The *cortical hormone concentration of the various animals* shows curious differences. Vars, Taylor and Pfiffner, 1934, reported the following "dog-units" per kilogram of gland: Mare, less than 165; horse, 1500; ox and dog, 2500; sheep and hog, 3500.

Clinical Efficiency in Addison's Disease.—Intramuscular injections of purified cortical extracts produce marked symptomatic improvement, especially in the early cases, although generally not so striking as in the acute deficiency of animals. Supplemented by sodium chloride administration, they are valuable for temporary alleviation of the crises. Their cost practically prohibits adequate continuous use, but it is doubtful whether they would postpone the final fatality indefinitely.

The effects of the injections are usually apparent within twenty-four to seventy-two hours and extend five to seven days after stopping the treatment. They are successively: (1) relief of the anorexia, nausea and vomiting; (2) reappearance of appetite and hunger sensation; (3) gain of weight, relief of fatigue, increase of strength and endurance; (4) apparent decrease of pigmentation (due to stretching of skin by dehydration, not to disappearance); (5) increased resistance to infection and to surgical procedures (Rowntree, Greene *et al.*, 1931; Harrop, Weinstein and Marlow, 1932). Hypertrophy of the breasts has been reported in the male patient during treatment with a cortex extract (R. A. Edwards *et al.*, 1938). This was presumably due to other hormones. *Adrenalectomy decreases the resistance of animals* to infections, toxins and many other poisons, excessive heat or cold, reduced barometric pressure, traumatic shock and, especially, severe burns. Injection of the extracts restores the resistance to morphine and histamine (Houssay and Marenzi, 1931) and tends to restore the other conditions toward normal; but effects on normal animals are doubtful (review, Swingle and Remington, 1944). The *gamma globulin* of the blood, the presumptive mother substance of the antibodies, is increased by administration of adrenotropic pituitary hormone or of the adrenal steroids (A. White and Daugherty, 1945). *Corticosterone* seems concerned especially with carbohydrate and other organic metabolism (review, Swingle and Remington, 1944).

Desoxycorticosterone.—It was isolated and synthesized by T. Reichstein *et al.*, 1937, and is used as the ester, *desoxycorticosterone acetate.* Daily hypodermic injection prolongs the life of adrenalectomized dogs, even with low NCl income; its omission precipitates the deficiency symptoms, which disappear when it is resumed (Thorn and Eisenberg, 1939). Its administration to patients with Addison's disease, on constant fluid and mineral intake, increases the plasma volume and the total Na and Cl of the plasma, and lowers the potassium level if this was high (Thorn and Howard, 1939). It has no significant effect on the *carbohydrate metabolism* in adrenal insufficiency (Britton and Corey, 1940). The cortical steroids act somewhat on the *sex organs.* This may be important in early life and is probably responsible for virilism, feminism and precocious puberty in patients with adrenal cortical tumors. Conversely, all the *sex hormones*, estrogenic, androgenic and progestational, cause some degree of Na and Cl retention; but only progesterone prolonged the life of male dogs after excision of the adrenals (Thorn *et al.*, 1937, 1938).

Electrolyte and Water Balance.—The phenomena of cortical deficiency depend largely, but not exclusively, on changes in the sodium metabolism. The principle disturbance is inability of the tubular epithelium to reabsorb sodium from the glomerular filtrate (H. E. Harrison and Darrow, 1939), resulting in large loss of this element by the urine, and decrease of the concentration of NaCl and $NaHCO_3$ in the blood serum. The excretion of water is increased, though not to the same degree as that of sodium. The depletion of this fluid from the blood and tissue spaces produces dehydration shock and oliguria. This is precipitated in Addison's disease patients and in adrenalectomized animals by salt restriction, and relieved by salt administration (review, R. F. Loeb, 1936). In compensation for the sodium loss, the urinary excretion of *potassium* is diminished in adrenocortical deficiency, and its concentration in the blood tends to rise (W. D. Allers, 1935). The rise in the K:Na ratio may be partly responsible for the deficiency symptoms (Zwemer and Truszkowski, 1936). Such individuals are hypersusceptible to potassium administration (E. C. Kendall and Ingle, 1937). *Administration of cortical extract to patients with Addison's disease*, or to adrenalectomized animals, promptly diminishes the excretion of sodium and of chloride and increases that of potassium, much more than in normal individuals. These effects are also produced by the isolated principles, especially by desoxycorticosterone; and by estrogens, progesterone and testosterone (F. A. Hartman, Thorn *et al.*, 1937; review, Swingle and Remington, 1944; J. P. Peters, 1944).

Impaired kidney function after removal of the adrenal cortex and in severe Addison's disease entails various other complex changes, including rise in blood urea, decreased phenolsulfonephthalein output, and in later stages retention of sulfate, phosphate and creatinine. The urea retention may occur before any clinical symptoms and while the urine volume is not decreased. Adrenalectomized animals are highly susceptible to *water intoxication* (Swingle, Parkins *et al.*, 1937), probably through inadequate urinary excretion, the ingested water being retained as extracellular tissue fluid (R. A. Shipley, 1945). In the later stages, dehydration is largely responsible for impairment of kidney function (E. K. Marshall and Davis, 1916). Support of diuresis by injection of isotonic *dextrose or glycerin solutions* somewhat defers death after adrenalectomy; but it is not comparable to sodium chloride (Marine and Baumann, 1927). Excision of the adrenals often lowers the *blood sugar level*, and the liver and muscle glycogen, especially when the food intake is poor. This is prevented by administering sodium chloride (C. N. Long *et al.*, 1940). It is probably due to deranged protein catabolism. The *oxidation of dextrose* is also disturbed, accounting partly for the muscular weakness. Adrenalectomy prevents the development of *fatty liver* after pancreatectomy, fasting or phlorhizin poisoning (Verzár *et al.*, 1938).

The electrolyte and water balance of normal animals is affected in the same direction, but not so potently, by *desoxycorticosterone*. This protects also against the effects of excessive water ingestion (R. O. Gaunt, 1943). Excessive doses are deleterious, even in adrenal deficiency, by retention of sodium and water and by loss of potassium, especially from muscle cells, leading to degeneration of cardiac muscle and electrocardiogram changes (W. Raab, 1942). Adrenal cortical extract and corticosterone have little effect on the normal balance (D. C. Darrow and Miller, 1942). Administration of desoxycorticosterone does not influence the course of *potassium auto-intoxication* by ureteral ligation (A. W. Winkler *et al.*, 1942).

Overdosage with desoxycorticosterone, especially if long continued, leads to increase of plasma volume, without tissue edema (Selye and Hall, 1943), but with polydipsia and polyuria, simulating *diabetes insipidus*, except that pituitrin is not fully effective (C. A. Winter and Ingram, 1943). Hypertension occurs clinically, generally returning to normal within two weeks after discontinuance (Perera *et al.*, 1944). Animals develop renal tubular hypertrophy and glomerular sclerosis (Selye and Hall, 1943). If de soxycorticosterone is given with sodium chloride, severe *motor disturbances* arise and progress to complete paralysis and death. They disappear on salt withdrawal, although the sterone is continued (Selye and Hall, 1943). Under certain conditions, rats develop polyarthritis resembling acute rheumatic fever, Aschoff bodies in the heart, and sometimes periarthritis nodosa (Selye, Sylvester *et al.*, 1944). Changes in the thymus and spleen are described by Selye, 1941. The *adrenal cortex* undergoes marked involution in male cats, but not in females (E. L. Sarasan, 1943); large doses of progesterone induce cortical involution in females, not in males; androgens much more readily in females. Estradiol produces marked hypertrophy, much more in males, inhibited by desoxycorticosterone, progesterone and testosterone (Selye, 1940). Desoxycorticosterone has *no carcinogenic action* in mice (Shimkin and Grady, 1941).

Pituitary adrenotropin controls the adrenal cortex as regards sugar, fat and protein metabolism, and to some extent its protective function against toxic substances, and probably its effects on muscle metabolism. It has apparently little effect on the electrolyte and water balance (H. G. Swann, 1940).

Lactation is completely inhibited by ablation of the adrenals and restored by cortical extract (J. L. Carr, 1931), but not by desoxycorticosterone (R. Gaunt, 1941).

Sodium chloride therapy of adrenocortical deficiency prolongs life after total excision of the adrenals (Stewart and Rogoff, 1925;

Marine and Baumann, 1927) and mitigates the nausea, fatigue and the other symptoms of Addison's disease, except the pigmentation. While it does not take the place of the hormone completely, it diminishes the requirements, possibly to the amount that the diseased gland can still manufacture. Usually some cortical extract must be given in addition to the salt. The latter should be administered in the dosage of 7 to 10 Gm. per day, in addition to what is normally taken in food (R. F. Loeb, Atchley and Stahl, 1935). Reduction of salt is likely to bring on a critical exacerbation. Potassium should be avoided.

Adrenalectomized rats develop a salt appetite, and this prolongs their survival time (C. P. Richter, 1936). Adrenalectomized dogs maintained by salt administration without hormone are hypersensitive to many substances not ordinarily toxic, and of course especially to potassium; so that 0.5 Gm. produces severe prostration. If the potassium income is increased gradually, considerable tolerance is established (Kendall and Ingle, 1937).

Mechanism of the Deficiency Symptoms.—The anhydremia and the change in the K:Na ratio are not an adequate explanation; for while the symptoms are in many respects analogous and are relieved by salt administration, nevertheless, the adynamia, hypotension, hypoglycemia, pigmentation, gastro-intestinal symptoms and neurologic disturbances are seen in Addison's disease patients when the sodium concentration of the blood is normal; and administration of cortical extracts to adrenalectomized dogs improves the symptoms strikingly before obvious changes occur in the urea, sodium or water content of the blood serum (Loeb and Atchley, 1937). Cortin maintains the life of adrenalectomized animals in the absence of the sodium-retaining hormone, in spite of the low plasma sodium (Hartman, Spoor and Lewis, 1939).

Capillary permeability, judged by Menkin's leukotoxin method, is inhibited by corticosterone, not by desoxycorticosterone; it is increased by estrone, diethylstilbestrol and progesterone (S. C. Freed and Lindner, 1941).

Therapeutic Use.—Extracts of adrenal cortex are used in the treatment of adrenal deficiency, 100 to 500 dog units per day for maintenance, 2500 to 5000 units in the crises, hypodermically, intramuscularly or intravenously. Oral administration is effective, but wasteful. The potency is assayed by survival of adrenalectomized dogs or rats (Cartland Kuizenga, 1936). Synthetic *desoxycorticosterone acetate* may be used as a reference standard (Grollman, 1939). This may also be employed clinically and is considerably cheaper than the extracts, especially if pellets are implanted under the skin (Thorn and Firor, 1940); a single implantation supplies the hormone for eight to twelve months. The supplementary sodium chloride income must be carefully regulated, as excess of this or of the hormone produces edema. *Histamine shock* in mice and rats may be prevented most effectively by desoxycorticosterone acetate together with parenteral injection of saline solution; treatment of established shock is much less successful (Perla *et al.*, 1940). *Traumatic and hemorrhagic shock*, however, is neither prevented nor mitigated by adrenal cortical preparations (K. A. Huizenga. Brofman and Wiggers, 1943; Swingle *et al.*, 1943). Venous limb occlusion shock is reported to give better survival with desoxycorticosterone acetate than with cortical extracts (I. H. Shleser and Asher, 1942).

Desoxycorticosterone acetate, U.S.P., is a white crystalline powder, practically insoluble in water, slightly in vegetable oils, sparingly in alcohol.

RENAL HYPERTENSIVE SUBSTANCE

The frequent clinical coincidence of renal vascular disease and hypertension suggests a causal relation, and Harry Goldblatt confirmed experimentally that continued restriction of the blood flow of a kidney results in persistent high blood pressure. It occurs with denervated kidneys and is therefore not nervous but humoral. It does not occur if a kidney is excised, so that the substanec must be formed in the kidney, probably by excessive production of the *renin* of Tigerstedt and Bergmann, 1898, (not to be confused with rennin!), which is found in saline extracts of kidneys, normal as well as ischemic. This is a proteolytic enzyme, which is not itself hypertensive, but reacts with a blood globulin, "hypertensinogen," to form a thermostable pressor substance *hypertensin* (Fasciolo), or *angiotonin* (Page), which acts directly on blood vessels. This is continuously destroyed in the blood, in the body and *in vitro*, by an enzyme, *hypertensinase* or *angiotonin inhibitor* (review, H. A. Lewis and Goldblatt, 1942; I. H. Page, 1940; Fasciolo *et al.*, 1940; terminology, E. Braun-Menendez *et al.*, 1943).

Renin, as contained in saline extracts of normal kidneys, produces a prolonged rise of blood pressure when it is injected intravenously (Tigerstedt and Bergmann). It is not constrictive in perfusion of excised organs unless blood plasma has been added (B. Friedman *et al.*, 1938). Only a small amount of renin is needed in ratio to the plasma substrate. It is nondialyzable and is destroyed by heat. It may be replaced by pepsin. It is present in the kidneys of all warm-blooded animals, but not in cold-blooded. Human renin appears somewhat specific (Braun-Menendez *et al.*, 1943).

The *plasma substrate* (*prehypertensin, preangiotonin, precursor, activator*), which is proteolyzed by renin to form the active substance, is probably a pseudoglobulin, probably formed in the liver. It disappears gradually in adrenalectomized dogs and is restored by administration of adrenal cortical hormones.

The *pressor substance* itself ("*hypertensin*" of Braun-Menendez, "*angiotonin*" of Page) is formed *in vitro* as well as *in vivo* by the digestion of blood plasma with renin. It is a thermostable, dialyzable substance, which has been isolated as a crystalline picrate. It constricts blood vessels directly. Its effects appear identical with those of experimental renal ischemic hypertension and of clinical "essential" hypertension, but it has not been shown that it is increased in the blood of hypertensive patients (Braun-Menendez). It is *destroyed* within a few minutes after injection, and also *in vitro*, by an enzyme, *hypertensinase* (angiotoninase, antiangiotonin, angiotonin inhibitor).

Repeated intravenous injection develops refractoriness (tachyphylaxis; Tigerstedt and Bergmann, 1898) partly by exhausting the store of globulin precursor, but perhaps also by developing an inhibiting substance (Page and Helmer, 1939).

Response to Drugs.—The blood pressure of dogs rendered hypertensive by the application of the Goldblatt clamp for one to two and a half months, could not be kept down by administration of estrone, testosterone, extracts of liver, pancreatic or adrenal cortex, pituitrin, tyrosinase, mannitol hexanitrate, thiocyanate, bromide, veratrum viride, acetylcholine, nicotinic acid, mistletoe, garlic or parsley. Intravenous injection of kidney extract produced about the same rise as in nonhypertensive controls (Wakerlin and Gaines, 1940; H. Goldblatt, Kahn and Lewis, 1942).

Urinary Hypotensive Substances.—Intravenous injection of many urines produces an acute fall of blood pressure resembling that of histamine. Several active extracts have been described, differing quantitatively in the susceptibility of various animals, in heat stability, and so on (review, R. R. Rigler, 1938).

Kallikrein is a hypotensive, noncrystallizable, nondialyzable, organic constituent of human and especially dog's urine, of unknown composition, destroyed by boiling and by strong acids and alkalis and oxidizing agents. It occurs also in pancreatic juice, saliva and blood.

Depressan is a heat-stable hypotensive substance obtained from boiled human urine (Wollheim and Lange, 1932).

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NITRITES, NITROGLYCERIN AND OTHER ALKYL NITRATES

Nitrites, nitrous esters and organic nitrates which are reduced to nitrites in the body, lower the tonus of arterial muscle, producing prompt fall of blood pressure. The action is directly on smooth muscle, and is mutually antagonistic with epinephrine. These drugs are used for relief of arterial spasm and other conditions of high blood pressure. They form methemoglobin in the body and *in vitro*.

Members.—The group comprises the inorganic nitrites ($NaNO_2$), the nitrous esters (amyl nitrite, ethyl nitrite, "Sweet Spirits of Niter"), and substances which liberate the nitrite ion within the body. Most important among the latter is glyceryl trinitrate (nitroglycerin or glonoin), which is easily broken up by alkalis into a mixture of nitrates and nitrites; a similar change occurs in the body. Erythrol tetranitrate and mannitol hexanitrate undergo analogous decompositions, but much more slowly. Even inorganic nitrates are reduced to a slight extent (Binz, 1901), especially by the putrefactive bacteria of the colon, and may then give rise to the phenomena of nitrite poisoning; but this requires large doses such as the quantities of bismuth subnitrate used in roentgen diagnosis.

Reduction of Nitrates to Nitrites.—It is generally assumed that the organic nitrates act only after being reduced to nitrites; but excised vessels react promptly to these nitrates so that they may perhaps act directly. It is also remarkable that the effective dose of glyceryl trinitrate is but a hundredth of that of sodium nitrite. On the basis of available nitrite ion, the fatal dose of sodium nitrite for rabbits with intravenous injection is at least twice that of the glyceryl trinitrate (Olman and Crandall, 1931). Presumably the organic esters penetrate more readily into the cells, and perhaps the reduction occurs only after their penetration, for they may depress blood pressure without increasing the nitrite concentration of the blood (Rath and Krantz, 1942; C. R. Marshall, 1945).

Composition and Action.—The nitrates of monohydric alcohols are less effective than the polyhydric. Nitroglycerin and erythrol tetranitrate act quantitatively alike when equimolecular doses are injected into a vein; by mouth the action of the erythrol ester is weaker and more prolonged, because it is much less soluble and therefore more slowly absorbed (Marshall, 1913). Krantz, Carr *et al.*, 1939, investigated the *nitrates of a series of sugar alcohols* for vasodepressor action on dogs. Ether linkage was found to diminish the potency but to prolong the action. *Isomannide dinitrate* resists hydrolysis and has the advantage that it dilates the coronary vessels (beef, rabbit and dog) without producing methemoglobin.

The relation of action to the constitution of aliphatic nitric and nitrous esters is reviewed by W. F. von Oettingen, 1946.

The nitrites fall into two groups according to the relative dominance of the two chief actions: The *vasodilatation* predominates with alkyl nitrites and alkyl nitro-substitution products. The introduction of OH and CO_2H groups into organic nitrates diminishes their vasodilator action (C. R. Marshall, 1912). *Methemoglobin formation* predominates with amido compounds and with aromatic nitro-substitution products.

Aromatic Nitro-Substitution Products.—The introduction of NO or NO_2 into the ring or side chain of cyclic hydrocarbons increases the toxicity. The reduction of the NO_2 of nitrobenzene to NH_2 (aniline) diminishes the toxicity; this is further decreased by introducing alkyl into the amido group. Stimulation and then paralysis of the central nervous system are marked with the nitro compounds, less with the amido compounds.

Actions on the Circulation.—The most important effect of the nitrites is a prompt fall of blood pressure, due to vasodilatation by direct action on the blood vessels.

Vasodilator Action.—This is first noticed in the skin of the face, in an area similar to that involved in blushing, but which may extend over the entire trunk to the ilium.

The *meningeal vessels* undergo dilatation at the same time. There is consequently redness of the face, heat and throbbing in the head, and headache. The flushing of the skin is brief, although it may considerably outlast the return of blood pressure. The headache is likely to persist, especially with erythrol tetranitrate.

The dilatation does not, however, remain confined to the skin, but spreads to other vessels, and relaxation of the splanchnic area in particular causes a speedy *fall of blood pressure* and a dicrotic pulse. The fall of blood pressure is due entirely to the extensive vasodilatation produced by the direct action of the nitrite on the arterioles and venules. The vasomotor center is not inhibited, but rather stimulated by the cerebral anemia (Pilcher and Sollmann, 1914). The total return flow of blood to the heart, and the auricular pressure, are not altered (C. J. Wiggers, 1918).

With inhalation of amyl nitrite, the effects are complicated by reflexes from its stifling odor and by central narcotic actions (Dautrebande, 1932). There is generally at first some reflex (vagal) slowing of the heart; but soon the *heart is greatly quickened,* so that a rise of blood pressure is frequently observed at the start (Hewlett, 1906), the dilatation being more than overcome by the quickened beat.

Evidences of Vasodilatation.—The vasodilatation can be demonstrated directly by inspection (the blushing); by plethysmographic measurements (Dossin, 1911) and by increased rate of vein flow. The fall of pressure occurs equally well when the cardiac changes are excluded by atropine.

Effects on Vein Flow and Vein Pressure.—In man, Hewlett, 1913, found increase of the volume, but scarcely of the blood flow, of the arm. Stewart, 1915, showed increase of the blood flow of the hand. There are also definite changes in the "pulse flow" (the flow during the cardiac cycle.). These occur when therapeutic doses are given in arterial tension, even when the blood pressure readings are not reduced (Hewlett, 1917). Burton-Opitz and Wolf, 1910, on injecting nitrite into the femoral artery of dogs, found the vein flow and vein pressure increased in the corresponding leg, while the general arterial pressure was practically unchanged. If amyl nitrite was inhaled, the vein flow in the leg decreased with the blood pressure, because of the withdrawal of the blood into the more powerfully dilated splanchnic vessels. Capps, 1911–1913, also found a fall of vein pressure.

Circulatory collapse occurs when the subject is in an upright position, from doses of sodium nitrite which have practically no effect in a recumbent position. The collapse is pronounced when the maximal blood flow through the hand has fallen to 20–40 per cent of the normal value. This is accompnaied by marked fall of vein pressure (S. Weiss *et al.*, 1937). The primary action appears to be on the venous side of the circulation, and raising the vein pressure increases the organ volume more than in normal subjects (Wilkins *et al.*, 1937).

Site of the Dilator Action.—Vasodilatation occurs after ligation of the blood vessels of the brain (Mayer and Friedrich, 1875); after destruction of the spinal cord (Lauder Brunton, 1869); in excised organs (Atkinson, 1888; Marshall, 1898, and later); and in excised arterial segments (Cow, 1911). The perfusion method shows that the vasomotor center is more commonly stimulated. The dilator action is therefore peripheral. Nitrites also relax other smooth muscle, without reference to their innervation. The action is therefore presumably directly on the contractile substance.

Antagonisms.—Nitrites are mutually antagonistic with most vascular constrictors: splanchnic stimulation (Bernheim, 1874), epinephrine, strophanthin, and others, raise the blood pressure during the nitrite fall; and conversely, nitrites lessen the rise of these constrictor agencies. The result is essentially an algebraic addition of the two opposed actions.

The antagonism is quantitative; *f. i.*, sciatic stimulation gives the same millimeter rise during as before the nitrites; and nitrites give the same millimeter fall during as before strophanthin, hydrastinine, pituitary, strychnine or ergot. This suggests that the point of attack of the nitrites is different from that of the pressor agencies (Pilcher and Sollmann, 1915). Cameron, 1906, proposed to utilize the antagonism for the bio-assay of epinephrine. He states that 0.6 mg. of nitroglycerin exactly neutralizes the pressor effect of 0.0075 mg. of epinephrine.

Lactate.—Perfusion of cat leg with sodium nitrite and also with acetylcholine often fails to produce vasodilatation until lactate is added (Densham, 1927).

The *capillaries* are dilated (microscopic observation) by the direct injection of undiluted amyl nitrite into the human skin (Carrier, 1922), but this may be due to local irritation.

The *vasomotor center* is not depressed, but rather is stimulated by its anemia; the stimulation, however, can not overcome the peripheral depression. This is shown by the perfusion experiments of Pilcher and Sollmann, 1915. Similarly, the blood pressure does not fall if a nitrite is introduced into the cerebral circulation, but prevented from reaching the systemic vessels. (Filehne, 1874, had concluded that the vasomotor center is depressed.)

The **heart** may be quickened during the fall of pressure, preceded by slowing in the event of amyl nitrite inhalation. Both effects are reflexes from the carotid sinus, but large doses also stimulate the cardio-inhibitory center directly (Heymans, Bouckaert and Regnier, 1933). The cardiac muscle is not affected directly to an important degree, but the coronary blood flow is increased by dilatation of the coronary vessels, and this together with the lowered resistance may improve the contractions of the weakened heart (review, H. D. Green, 1940). Generally the cardiac excursions are smaller because of the quickened rate. The size of the heart is markedly reduced (roentgenoscopy, Katzilambros, 1933). The blood pressure waves appear particularly low, because the pressure wave is more readily dissipated, on account of the dilatation. The pulse, on the other hand, may be bounding and dicrotic, because the arteries are emptied more completely during diastole.

The *tachycardia* is due mainly to reflex depression of the vagus center, for after section of the vagi, or after atropine, nitrites cause but little further acceleration (Mayer and Friedrich, 1875). The slight remaining quickening is abolished by dividing the accelerators (Dossin, 1911). The rate of the excised heart is not changed by nitrites (Plumier, 1905). The excitability of the vagus trunk to direct electric stimulation persists.

The depression of the vagus center is due to the fall of blood pressure, and not to a direct action of the nitrite, for no quickening occurs if the pressure is kept level by partial compression of the aorta (Filehne, 1879). The vagus center may still respond to strong reflex stimulation (Mayer and Friedrich).

Diagnostic Significance of the Heart Rate.—In normal man, the acceleration on inhaling amyl nitrite may be considerable, often to double. Practically all irregularities of impulse formation or conduction are either improved or exaggerated (D. Scherf, 1927). With complete heart block, the auricular rate is accelerated during the amyl nitrite fall of pressure; but the ventricular rate sometimes very little, or sometimes two or three times as much as the auricles (A. R. Gilchrist, 1934). In experimental partial heart block, the rate is still quickened by amyl nitrite (Fredericq, 1916).

Electrocardiograms.—When amyl nitrite is inhaled by intact dogs, there is at first a marked reflex increase of vagus tone, shown by slowing of the sinus rate, exaggerated sinus arrhythmia, lengthened A-V time or A-V block, and a negative tendency of the P and T waves. As the blood pressure falls, these changes are reversed. The vagus tone becomes depressed, the sinus rate is quickened, the arrhythmia and block disappear, and A-V time is shortened; the P and T waves become more positive. These phenomena are not affected by previous digitalization; however, large doses of nitrite abolish the ectopic beats due to digitalis (Halsey, 1917). The *excised mammalian heart* is scarcely affected by moderate doses, perhaps slightly stimulated, then depressed (Loeb, 1903; Plumier, 1905; Dossin, 1911). The *excised frog's heart* may be quickened by low concentrations (1:10,000); higher concentrations weaken (1:5000), or stop (1:1000) the contraction.

Coronary Vessels.—Increased outflow has been demonstrated in intact animals (F. Meyer, 1912; N. H. Boyer and Green, 1941); in Starling heart-lung preparations (Bodo, 1928); and in excised mammalian hearts (O. Loeb, 1903; L. N. Katz and Lindner, 1939). The coronary vessels are therefore dilated (also excised arterial rings; Voegtlin and Macht, 1913), and the coronary circulation is improved. This explains the beneficial action in angina pectoris.

Angina Pectoris.—The inhalation of amyl nitrite was introduced by Lauder Brunton in 1867. In *coronary spasm and sclerosis,* nitrites promptly give marked or complete relief of the pain and anxiety, and under their influence greater exertion may be undertaken before bringing on an attack. One to 3 drops of the promptly acting amyl nitrite are inhaled. It may be carried in thin glass capsules, "pearls," one of which is crushed in a handkerchief, as needed, or a tablet of glyceryl trinitrate (0.6 mg., 1/100 grain) may be dissolved under the tongue. This generally acts in one to three minutes and may be repeated every four minutes until relieved.

In coronary thrombosis and infarction, nitrites do not relieve the pain; indeed, they may aggravate it by the fall of pressure (Wearn, 1923; Prodger and Ayman, 1932; Wiggers and Green, 1936).

S. M. Smith, 1921, reported beneficial results from glyceryl trinitrate after closure of a coronary branch in dogs. The distal cyanosis tended to fade, and the blood flow from the distal end of the severed coronary arteries tended to increase.

Cardiac Insufficiency.—The relief of the heart from excessive resistance may render nitrites useful in these conditions. Glyceryl trinitrate (1 mg.) is used, generally in combination with digitalis.

Use against Arterial Hypertension.—The vasodilating action of the nitrites tends to relieve the headache and other symptoms, and the relief lasts somewhat longer than the fall of blood pressure; but nitrites fail to lower the pressure in arterial sclerosis, and also often in severe essential hypertension, perhaps because the dilator action is automatically compensated by increased central tone. In any case they usually lose their efficiency after a short time. Increasing the dose produces unpleasant symptoms—headache, restlessness, sometimes dyspnea. They must therefore generally be alternated with venesection, sweating, nauseants, and the like. The effect of these is usually less marked, but more lasting (J. L. Miller, 1910; C. H. Lawrence, 1912). Glyceryl trinitrate appears to be the most useful; amyl nitrite may lower the pressure when glyceryl trinitrate fails, but it causes more headache. Erythrol tetranitrate often causes intense headache. Sodium nitrite is said to give least headache (Hewlett, 1912), but is liable to upset digestion. Mannitol hexanitrate is not successful in maintaining normal blood pressure in animals with experimental renal ischemia (H. Goldblatt *et al.*, 1942).

Some tolerance usually develops if the administration of glyceryl trinitrate is continued, often in two or three days. The dosage must then be increased or the response disappears. Suspension of the administration for a few days may restore the susceptibility (also with rabbits; Myers and Austin, 1929). Matthew claims that the tolerance is not acquired with sodium nitrite or erythrol tetranitrate.

Rapidity and Duration of Action.—This constitutes the principal difference between the members of the group and varies greatly with individuals. The differences are due chiefly to absorption, for all act essentially alike when injected by vein (J. H. Wills *et al.*, 1944). Amyl nitrite, when inhaled, acts in ten to fifteen seconds, the action disappearing again within seven minutes. For the others, with the usual oral clinical doses, the onset and duration average respectively: glyceryl trinitrate, two and twenty minutes; sodium nitrite, seven and sixty-two minutes; erythrol tetranitrate, thirty-five and 260 minutes; mannitol hexanitrate, fifty-five and 252 minutes (J. C. Weaver *et al.*, 1944).

The extent of the fall increases with the dosage, the increase becoming progressively smaller. The duration of the action is not so much influenced by the dosage. The fall of systolic pressure in hypertensive patients averages: glyceryl trinitrate, 6 mg., 16 mm.; sodium nitrite, 130 mg., 21 mm.; erythrol tetranitrate, 16 mg., 14 mm.; mannitol hexanitrate, 32 mg., 12 mm. The diastolic fall is half or less. Normal individuals show generally less effect. The reliability of therapeutic response depends rather more on the rapidity of action than on the average fall (J. H. Wills *et al.*, 1944).

Administration.—The dosage of the nitrites should be kept as low as possible, to prevent the rapid development of tolerance. It is best to give just enough to cause a slight quickening of the pulse and feeling of fulness in the head; or a fall of systolic pressure of not more than 30 mm. This dose may be given four times a day. The initial dose may be 0.5 mg. ($\frac{1}{100}$ grain) of glyceryl trinitrate, increasing gradually. The equivalent doses of the other nitrites are shown in the preceding paragraph. The treatment may be intermitted for a few days in every two or three weeks, starting again with a smaller dose. Hypodermic injections are rarely needed, the drugs being readily absorbed. Glyceryl trinitrate is materially more potent when it is absorbed from the tongue than when it is swallowed. In the latter case it is absorbed into the portal circulation and destroyed by the liver. (For this reason, about twenty times as much is required to lower the blood pressure when it is injected by a vein that empties into the portal system, such as the splenic, than by a vein which avoids the portal circulation, such as the femoral.)

Bismuth Subnitrate as a Conveyor of Nitrite Action.—This was advocated by E. J. Stieglitz, 1930, in hypertension (0.65 Gm. three times daily), to furnish a continuous supply of nitrite by its reduction in the colon. Bruen, 1934, however, could not demonstrate any effect on the blood pressure and other symptoms, with the largest practicable therapeutic doses. The small quantities ordinarily absorbed are probably bound by the liver. Serious poisoning sometimes occurred from the large doses formerly used in roentgenoscopy.

Nitrite Headache, Meningeal Congestion, Cerebrospinal Fluid Pressure, Brain Volume.—The headache produced by nitrites is due primarily to meningeal congestion. The pia vessels dilate (confirmed by microscopic observation through trephine opening; H. G. Wolff, 1929), by the direct action of the nitrite upon them, notwithstanding the fall of arterial pressure. The brain volume increases (observed in man through trephine opening; Raphael and Stanton, 1919). The pressure of the cerebrospinal fluid rises (W. D. Paul and Greene, 1936). On the other hand, *migraine* sometimes yields to nitrite, presumably when it was connected with arterial spasm. Occasional benefit has also been reported in *epilepsy*.

Intra-ocular tension is raised by amyl nitrite, even when the general blood pressure is lowered (Wessely, 1915). This enjoins caution when using nitrites in *glaucoma*. The *retinal vessels* are also dilated (Hirschfelder, 1915). Amyl nitrite may produce the appearance of *yellow spots* in the visual field. The mechanism is not clear.

Hemostasis.—Nitrites have been tried against *internal hemorrhage*, on the assumption that the lowered blood pressure would tend to arrest bleeding and permit the formation of a clot; but the bleeding would be favored by the direct dilator action. The resultant of these opposite tendencies is difficult to foresee, and probably varies with different conditions. Nitrites would therefore be unreliable remedies. Experimentally, Frey, 1909, found a slight increase of pulmonary hemorrhage; Lisin, 1907, claimed diminution of intestinal hemorrhage. *Capillary hemorrhage from superficial wounds* is increased by the systemic administration of nitrites, notwithstanding the fall of pressure (Hanzlik, 1918).

Respiration is accelerated (Mayer and Friedrich), probably by the changes in the blood and circulation. The *bronchial muscles* are relaxed by nitrites (Doyon, 1906; excised, Titone, 1913; surviving lungs, Baehr and Pick, 1913). This may explain their *use in asthma;* but the action is not sufficient to combat anaphylactic bronchial spasm in guinea pigs (Barlow and Beams). The smoke of the "Charta Potassii Nitratis" (paper impregnated with saltpeter) probably owes a part of its effect to nitrite compounds. The *pulmonary vessels* are not markedly dilated; indeed, Macht, 1914, found constriction in excised pulmonary arteries. The pressure in the pulmonary artery is generally slightly increased (literature in Wiggers, 1911). The rise is probably due partly to the engorgement of the large veins. The *nasal mucosa* becomes congested when glyceryl trinitrate is administered, even before the blood pressure falls (Walton and Kehr, 1928). Amyl nitrite inhalation in dogs may give either slight dilatation or considerable constriction (D. E. Jackson, 1927).

Gastro-Intestinal Tract.—Amyl nitrite inhalation promptly inhibits *gastric peristalsis* and tonus, the effect being greatest when the cutaneous flush is felt in the face. The peristalsis returns to its previous activity with equal promptness, in about three minutes after the inhalation is stopped (Todd, 1930). This is used in roentgenology for relaxing pyloric spasm (G. W. Holmes and Dresser, 1928; Beans, 1931), and for the relief of colic pain, for it has a similar effect on the intestines. Hirschfelder, 1915, reported that the systemic administration of nitrites relaxes the intestinal constriction produced by lead salts. It has been used clinically in lead colic, but with limited success. Sodium nitrite, 0.064 Gm., delays the emptying time of the stomach by an average of 24 per cent, but with marked individual variations (Sleeth and Van Liere, 1941). It may also cause some gastric irritation by the liberation of nitrous acid, but generally not sufficient to interfere with its therapeutic use. There is also some slight interference with the digestive ferments (Hale, 1910). A. Bergman, 1929, reported increased volume of gastric juice during the first hour after its injection, with diminished total and free acidity.

Other smooth muscle is generally relaxed in excised organs, by sufficiently high concentrations; for instance, the *ureter* (Macht, 1917) and the *gallbladder* (Lieb and McWhorter, 1915); but the relaxant action is not sufficiently powerful to be effective against the colics caused by obstruction of the bile ducts, ureters or urethra.

Urine.—The variations produced in the secretion of urine appear to be purely secondary, and depend upon whether the renal arterioles or those of the general circulation are relatively more dilated; the former cause an increase, the latter a diminution, of urine.

In patients with excessively high blood pressure, the nitrites generally increase, some times considerably, the excretion of urine, nitrogen, total solids and phenosulfonphthalein (Lawrence, 1912).

Metabolism.—The effects were studied by Surveyor, 1906.

Temperature.—The dilatation of the skin vessels increases the surface temperature (as much as 3° C. in the blush area; Lahnstein). There is a corresponding increase of heat loss, but this is compensated in normal individuals, at least for small doses, so that the normal temperature is not affected. In fever, however, there is a distinct antipyretic effect (Jacobj, 1913; Krauss, 1913). Ethyl Nitrite, as "Sweet Spirits of Niter," has been used popularly as a diaphoretic and diuretic. Its action is not very energetic. Large doses of nitrites also lower the normal temperature by depressing the circulation.

Methemoglobinemia.—Excessive doses of nitrites form methemoglobin (Gamgee, 1868), which causes cyanosis and asphyxia. The animals generally recover since the blood corpuscles are not destroyed. It is significant as a factor in nitrite poisoning. It is utilized in the treatment of cyanide poisoning, to form the nontoxic cyanhemoglobin.

One molecule of nitrite reacts with two of hemoglobin to form two of methemoglobin, *in vitro* and presumably *in vivo* (L. A. Greenberg *et al.*, 1943). The change to methemoglobin is preceded by a short induction period, followed by a rapid reaction. With excess of nitrite, part of the methemoglobin forms nitric oxide hemoglobin (W. Marshall and Marshall, 1945). If sodium nitrite is administered by vein to dogs, the methemoglobin reaches its maximum in five minutes to an hour, and disappears again completely in a few hours. The amount formed is *proportional to the dose.* Death occurs from this cause with 50 mg. per Kg. of body weight (Hug, 1933).

The methemoglobinemia can be removed by intravenous injection of *methylene blue,* 1 to 2 mg. per Kg., or orally every four hours, clinically (A. F. Hartmann, Perley and Barnett, 1938) and in animals (A. P. Richardson, 1939).

Red blood corpuscles absorb nitrite ions, with removal of chloride ions. The entrance of the nitrite ions is retarded by certain anions (Rohonyi, 1916).

The *red color of corned beef*, produced by pickling with saltpeter (potassium or sodium nitrate), is due to formation of nitrite and its combination with the myohemoglobin (R. H. Kerr *et al.*).

Fate.—Nitrite leaves the blood stream rapidly, even before the recovery of the blood pressure (Crandall, Leake *et al.*, 1929). Some 60 to 70 per cent disappears in the body, partly by oxidation. The fate of the remainder is not known. A small amount (1:100,000,000) is reported to be normally present in the blood, saliva and sweat, but not in the cerebrospinal fluid or urine (E. J. Stieglitz and Palmer, 1937).

Toxicology.—Mild nitrite poisoning may occur from therapeutic overdosage or *hypersusceptibility*. Nervous and anxious patients may react with rise of pressure and tachycardia (G. Richard, 1921), presumably due mainly to excitement. Others may react by marked cardiac slowing and alarming syncope, even after small doses. The severity of the headache is variable. Other side actions which may occur are localized edema, excessive sweating, and visual disturbances (Cornwall, 1913). On the other hand, tolerance is sometimes quite marked. More serious poisoning has occurred accidentally, in the roentgenologic use of bismuth subnitrate and industrially with nitroglycerin. The *treatment of nitrite poisoning* is directed chiefly against the methemoglobin asphyxia, and the low blood pressure. The patient should be kept recumbent, with the head lowered. Epinephrine should be injected, to raise the blood pressure and to mobilize unpoisoned blood compounds from the spleen. Oxygen should be inhaled. Transfusion of blood may be life saving.

Toxic Symptoms from Sodium Nitrite.—Rüegg, 1935, reported three severe cases, when nitrite was taken in mistake for salt. Another outbreak, with a fatality, is reported by M. Greenberg *et al.*, 1945. The symptoms are prompt nausea, vomiting, cyanosis (methemoglobin), collapse, loss of consciousness for several hours, usually with recovery. The symptoms in animals are similar to those from nitroglycerin (Dossin, 1911). The *toxic effects of amyl nitrite* are also similar (Rosen, 1888).

Toxic Effects of Nitroglycerin.—Its extensive use as an explosive makes these especially important. Overdoses produce nausea, vomiting, colic, and sometimes bloody diarrhea. The skin is flushed and perspiring. There is vertigo and persistent throbbing headache; rarely blindness and delirium. The respiration is first hyperpneic, then dyspneic and slowed. The surface becomes cold and cyanotic; the pulse is gradually slowed, dicrotic and intermittent. Paralysis sets in, and is followed by clonic convulsions. The reflexes are lost. Death occurs by failure of respiration, after four to seven hours. The *fatal dose* varies greatly. D. D. Stewart, 1905, reported a patient in whom 20 grains of absolute nitroglycerin produced only slight effects. Nitroglycerin is readily absorbed, even from the intact skin, and persons engaged in its manufacture suffer severely from headache during the first few days. After this, however, they appear to be quite unaffected, unless they leave work for several weeks and then resume the occupation. The work is said to be not unhealthful. The *local action* on the hands may result in skin eruptions and ulcerations.

Smokeless gunpowders (nitroglycerin, nitrocellulose, and the like), when exploded, liberate gases which produce the combined effects of nitrites, asphyxia and pulmonary edema. The principal products are NO_2 (nitrogen peroxide) and CO (Kiefer, 1905). The vasodilatation and tachycardia are followed by persistent headache ("powder headache"), which does not yield to acetanilid, and so on, but is best treated by strong coffee, and poultices applied to the back of the neck.

Sodium nitroprusside, sodium nitroferricyanide, $Na_2Fe(NO)CN_5.2H_2O$, acts chiefly as the nitrites, small doses causing prolonged fall of blood pressure, without producing methemoglobin. Very large doses may possibly form cyanide (L. Hermann), and as this might imaginably occur with moderate doses (although it has not been demonstrated), its therapeutic use does not appear advisable. It is used as a reagent and occurs in dark red crystals, freely soluble in water. Alkalis decompose it into ferric hydroxide, sodium nitrite and sodium ferrous cyanide. The fall of pressure occurs promptly after oral administration of 5 mg. per Kg., hypodermically with 0.05 mg. per Kg., and intravenously with 0.001 mg. The heart is accelerated by the fall of blood pressure. The symptoms in fatal poisoning are vomiting, rapid respiration and rapid pulse (with arterial color of the blood); excitement, tremors, muscle twitching, convulsions of medullary type; dyspnea, cyanosis, mydriasis, collapse, cardiac arrest. The symptoms are probably due largely to cerebral anemia from the low blood pressure. Artificial respiration postpones death (Johnson, 1929).

Hydroxylamine (NH_2OH) is decomposed in the body into nitrite and ammonium. It produces the effects of both these substances (methemoglobin formation, convulsions, central paralysis, Lewin, 1889).

PREPARATIONS.—***Amyl Nitrite, U.S.P** (Amylis Nitris), a clear, yellowish liquid, containing not less than 80 per cent $C_5H_{11}NO_2$ (chiefly iso-amyl nitrite); peculiar, ethereal fruity odor and pungent, aromatic taste; is almost insol. in water, miscible with alc. or ether, very volatile, even at low temperatures, and inflammable. Dose, by inhalation, 0.2 cc., 3 minims. It may be carried in thin glass capsules, "pearls," one of which is crushed in the handkerchief as needed.

Sodium Nitrite, U.S.P., is freely sol. in water. Dose, 0.03 to 0.12 Gm., $\frac{1}{2}$ to 2 grains. *Sodium Nitrite Tablets*, U.S.P.; usual sizes, 30 and 60 mg., $\frac{1}{2}$ and 1 grain.

***Glyceryl Trinitrate Tablets,** U.S.P. (Nitroglycerin, Trinitrin or Glonoin); the usual sizes contain 0.3, 0.4, 0.6 and 1.2 mg. ($1/200$, $1/140$, $1/100$ and $1/50$ grain). Average dose, 0.4 mg. The drug is not volatile and the tablets do not deteriorate rapidly (Rippetoe and Smith, 1914). E. L. Sagall *et al.*, 1946, found no recognizable difference in clinical effectiveness between fresh tablets and those eleven years old, unless they were exposed to excessive heat (37° C.). *Spirit of Glyceryl Trinitrate* (Liquor, B.P.) is an alcoholic 1 per cent solution. Miscible with water and alc. Explosive when allowed to dry. (If any considerable quantity is spilled, a solution of sodium or potassium hydroxide should be poured over it immediately.) Dose. 0.03 to 0.12 cc., ½ to 2 minims. *Erythrityl Tetranitrate Tablets* (Erythrol Tetranitrate, Tetranitrol) contain 0.015 or 0.03 Gm., ¼ or ½ grain, of $C_4H_6(NO_3)_4$ each.

(*Pentaerthrityl Tetranitrate,* "PETN," used in munitions, produces nitrite effects, with relatively low toxicity; von Oettingen *et al.*, 1944.)

Mannitol hexanitrate, N.N.R.; $H(CHONO_2)_6H$, mixed with carbohydrate substances to render it practically nonexplosive. Dose, 16 to 32 mg. at intervals of four to six hours. Absorption is incomplete (L. A. Heppel, 1941). *Tablets,* 16 and 32 mg.

Ethyl Nitrite Spirit, N.F. (Spirit of Nitrous Ether, Sweet Spirit of Niter), is a pale yellowish alcoholic solution of about 4 per cent ethyl nitrite ($C_2H_5NO_2$). Deteriorates readily, unless stored in filled amber-colored bottles. Incompatible with antipyrine, morphine and iodides. The addition of water throws ethyl nitrite out of solution; it then evaporates rapidly, lowering the strength (E. R. Squibb, 1889). Dilution should be made shortly before administration (Marshall and Gilchrist, 1915). Dose, 2 cc., 30 minims, as diaphoretic.

DIGITALIS GROUP

Digitalis, Strophanthus, Squill, Apocynum, Barium and a number of other drugs increase the tonus, excitability and contractility, and the refractory phase of the cardiac muscle, stimulate the vagus center and slow the conduction through the His bundle. With therapeutic doses, these actions result in slower but more powerful beats of the heart, which bring about compensation in valvular cardiac lesions and thus relieve the symptoms—the irregularities, edemas, congestions, dyspnea, and so forth. Under these conditions, there is often marked diuresis. The blood pressure is generally unchanged in man, usually increased in animals. The vagus center may also be stimulated, especially by toxic doses, partly directly, partly through the rise of blood pressure. The tone of the arterial muscle is increased. The effects set in slowly on oral administration; almost immediately on intravenous injection. They tend to be fcumulave, and to outlast the administration or a considerable time. Toxic doses produce vomiting, cardiac irregularity and sudde heart failure. The recognition of these toxic effects is important, since they often arise from the cumulative action. The members of the group are local irritants. Their hypodermic injection is painful. Their absorption from the gastro-intestinal canal is slow and often uncertain. The active principles are generally neutral glucosides, and therefore rather unstable, especially in acid, aqueous solutions. Digitalis contains several distinct glycosides with similar actions. The various "strophanthins" are derived from several related plants. They differ in activity and toxicity according to their origin. All the characteristic digitalis effects are produced by all the members of the group, so that a single description will suffice. The differences between them are only quantitative. So far as they are known, they will be pointed out as occasion arises.

Drugs Producing Digitalis Effects.—A considerable number of drugs containing glycosides with "digitalis" action are used in medical practice, such as Digitalis, Strophanthus, Squill and Apocynum. Of less practical importance are Helleborus, Adonis, Convallaria, Thevetia, Oleander, Cheiranthus, Uzaria, Antiaris toxicaria (the Upas tree of Java; Chopra and De, 1934). Several *arrow poisons,* chiefly African, contain digitaloid glycosides: strophanthin, ouabain, antiarin, acocantherin, and so on (Trendelenburg, 1909). The toxic principles found in the skin and blood of the common *toad* and other toad species, bufotoxin, bufagin and bufotalin, are closely related to the digitalis glycosides in structure and action. *Erythrophleine,* a glycosidal alkaloid, can be counted in the group. Other alkaloids—veratrine, caffeine, curine, epinephrine—remind somewhat of digitalis, but are not typical. Barium salts, calcium ions, alkaline hydrates and even normal saline solutions produce cardiac actions which resemble those of digitalis, but the resemblance may only be superficial.

The **cardiac glycosides** consist of a sugar molecule, of unique structure in some cases and an "aglycone" or "genin," closely related in the different principles of the variousplants, composed of a cholanic (cyclopentane phenanthrenic) nucleus with seventeen carbons and an unsaturated lactone side chain with four or five carbons, which is essential to the action. The sterols, including the sexual hormones, also have a cholanic nucleus, but lack the lactone and the digitalis action (reviews, W. A. Jacobs, 1933; Tiffeneau, 1937). The genins (digigenin, and others) are responsible for the digitalis actions. The sugars influence the penetration. The aglycones are generally less potent on the heart than are the corresponding glycosides, and their action is shorter

(Chen, Robbins and Worth, 1938). The glycosides are distinguished by a latent period before they act, and by long persistence in cells (Straub). They are difficult to isolate, and are usually distinguished mainly by their solubility, stability and absorbability. These vary, however, with conditions, with the methods of extraction and with different specimens of the drug (E. Meyer, 1917). This has been responsible for much confusion.

Active Principles of Digitalis Leaf.—Three cardiac glycosides, the (crystalline) *digitoxin*, and the (amorphous) *gitalin* and *gitoxin*, have been isolated chemically pure from the dried leaves of the official Digitalis purpurea (review, A. Stoll, 1937). They total about 1 per cent of the leaf. The other cardiac principles which have been claimed for the official leaf are probably impure mixtures of the above. Digitalis, however, also contains saponins (*digitonin*, *digitsaponin* and *gitonin*), which do not produce the typical cardiac effects, but probably modify the solubility of the other principles. The cardiac glycosides have identical actions, and differ biologically only in the intensity and duration of their effects, and physically in their solubility in different solvents, and this is modified by conditions. Although pure digitoxin is but slightly soluble in water, hot or cold water extracts practically the entire glycosides from the leaves, probably with the aid of the saponin.

Digitoxin is the best characterized and probably the most important of the principles of digitalis leaf, in activity and in quantity (0.22 to 0.4 per cent). It does not occur in digitalis seed. It was isolated by Nativelle, 1869, and called "Digitaline cristallisée." Its analytical investigation was completed by A. Windaus and Stein, 1928. It occurs as crystals, soluble in alcohol and in chloroform, but difficultly soluble in water (when pure) and in ether. In the presence of other substances, even of water, the solubility characters of digitoxin are considerably modified, perhaps by converting it into colloidal forms. It is quite conceivable that some of the principles of the other groups may be physical modifications or compounds of digitoxin. *Digitophyllin*, Kiliani, is perhaps a similar crystalline principle of the leaves. *Anhydrogitalin*, Kraft, is also a closely related constituent of digitalis infusions.

Gitalin was isolated by Cloetta and investigated by Windaus. It is amorphous, soluble in water and more so in chloroform; and is the constituent extracted from the cold aqueous solutions by chloroform.

Kiliani, 1914, found that the gitalin of Kraft, 1912, is a mixture. S. Weiss and Hatcher, 1923, found that the ether-soluble portion of gitalin contains a fraction which gives the reactions of digitoxin, and is so rapidly absorbed that the clinical effect occurs promptly on oral administration (Eggleston, 1920); but it is also excreted so rapidly that the effective dosage is relatively high.

Gitoxin was isolated by Cloetta and by Kraft, and the formula established by Windaus. *Digitalein* of Schmiedeberg and of Kiliani (1913 and 1914) are probably mixtures containing chiefly gitalin. They are soluble in water, but relatively insoluble in chloroform. Most of the commercial products intended for intravenous injection, such as *Digalen*, *Digipan*, *Digipuratum*, *Digitalysatum*, *Verogen* are of this type (Straub; Krehl, 1919).

The *digitalis saponins* are readily soluble in water, slightly soluble in alcohol and lipoid solvents. The *crystalline Digitonin* Kil. was considered a definite substance, which can be split into a hexose and digitogenin; but Windaus and Schneckenberger, 1913, considered it a mixture, from which they isolated *Gitonin*. The *amorphous Digitonin* Schm. (*Digitsaponin*, Kraft) is probably a mixture of the crystalline with several amorphous saponins (Kraft). The digitonins produce, not the digitalis effects, but the irritant and hemolytic properties of the saponin group. The digitsaponins of the leaves are not hemolytic (Kobert, 1912). Digitonin and its decomposition products are discussed by Windaus and Weil, 1922.

Inactive Principles.—A number of these have been isolated, such as the crystalline glycoside *gitin* and *digin*, Kraft, 1912, from the leaves.

The name *Digitalin* has been applied to a number of dissimilar products. The resulting confusion is so dangerous that the term is not employed by modern workers; it must never be used without designating the kind of digitalin that is meant.

The original *Digitalinum Verum* of Schmiedeberg and Kiliani consisted of those amorphous glycosides of the seeds that are soluble in alcohol, but little soluble in water, chloroform and ether.

Commercial digitalins are impure, often variable, mixtures of digitalis principles. *Digitalin "Amorphous"*; generally means French or Belgian digitalin (digitalin chloroformique); uncertain composition; insoluble in water (perhaps mainly Digitalin, Schm.). *Digitalin "Crystallized"*; objectionable synonym for Digitonin; for Nativelle (French); and for Digitoxin. *Digitalin "Homolle"*; mixture of glycosides; mainly true Digitalin; practically insoluble in water. *Digitalin "Nativelle"*; crystalline, probably mainly Digitoxin. *Digitalin "German"*; amorphous mixture from seed; contains principally Digitonin (50 to 60 per cent) and some Digitalinum verum (5 to 6 per cent), and Digitalein. Soluble in water or alcohol.

Digitalis seeds contain different but related glycosides, among them the *Digitalinum verum* of Schmiedeberg and of Kiliani This is usually amorphous, but may be obtained as crystals. It is sparingly soluble in water, but is dissolved by the saponins.

Digitalis lanata, another species of the plant, indigenous in the Balkans, yields gitoxin and a new glycoside, *digoxin* (Sidney Smith, 1930), and perhaps others.

Native Digitalis Glycosides.—Stoll and Kress, 1933 (review, Stoll, 1937), find that the glycosides of dried digitalis are themselves cleavage products of glycosides, "digilanids," which may be isolated by special precautions from the fresh leaves of D. purpurea, but especially of lanata, where they exist as tannoids. The crystallized glycosides can be separated by immiscible solvents into three fractions. Enzymes contained in the digitalis leaves split off glucose and thus yield the ordinary glycosides, digitoxin from digilanid A, gitoxin from B, and digoxin from C, which is absent from purpurea. A and B differ from C by the absence of an acetyl group (hence, desacetyl digilanids).

Cleavage Products (Aglycones and Sugars) of the Digitaloids.—The close relationship is illustrated by the following tabulation (adapted from Straub). All the *genins,* except Scillaridin, have twenty-three carbons, thirty-two to thirty-six hydrogens, and three to six oxygens. All but bufagen, convallamarin and scillarin have unsaturated lactone groups, which explains their tendency to decompose spontaneously. The *sugars* are chiefly dextrose, rhamnose and four alpha-deoxy sugars, digitoxose, cymarose, digitalose and sarmentose, which have so far been found only in the cardiac glycosides. They render the glycoside more readily oxidizable (Jacobs and Bigelow, 1932). Digitoxose is responsible for the Keller-Kiliani color test.

IMPORTANT CARDIAC GLYCOSIDES AND THEIR CLEAVAGE PRODUCTS

Digitaloid			*Aglycone (Genin)*			*Sugar*	
Digilanid A	$C_{47}H_{74}O_{18} + H_2O$	=	Digitoxin	$C_{41}H_{64}O_{13}$	+	Dextrose	$C_6H_{12}O_6$
Digitoxin	$C_{41}H_{64}O_{13} + 3H_2O$	=	Digitoxigenin	$C_{23}H_{34}O_4$		3 Digitoxose	$3(C_6H_{12}O_4)$
Gitalin	$C_{35}H_{56}O_{12} + 2H_2O$	=	Gitoxigenin hydrate	$C_{23}H_{36}O_6$	+	2 Digitoxose	$2(C_6H_{12}O_4)$
Gitoxin	$C_{41}H_{64}O_{14} + 3H_2O$	=	Gitoxigenin	$C_{23}H_{34}O_5$	+	3 Digitoxose	$3(C_6H_{12}O_4)$
Digitalinum	$C_{36}H_{56}O_{14} + 2H_2O$	=	Gitoxigenin * (but see below)	$C_{22}H_{34}O_5$	+	Dextrose probably attached to the digitalose Digitalose (methyl ether of methy pentose)	$C_6H_{12}O_6$ $C_7H_{14}O_5$
Oleandrin	$C_{30}H_{46}O_9 + H_2O$	=	Gitoxigenin†	$C_{23}H_{34}O_5$	+	Digitalose	$C_7H_{14}O_5$
Strophanthin K	$C_{36}H_{54}O_{14} + 2H_2O$	=	Strophanthidin	$C_{23}H_{32}O_6$	+	Dextrose and Cymarose	$C_6H_{12}O_6$ $C_7H_{14}O_4$
Cymarin	$C_{30}H_{44}O_9 + H_2O$	=	Strophanthidin	$C_{23}H_{32}O_6$	+	Cymarose	$C_7H_{14}O_4$
Scillaren A	$C_{36}H_{52}O_{12} + H_2O$	=	Scillaridin	$C_{24}H_{33}O_3$	+	Dextrose and Rhamnose	$C_6H_{12}O_6$ $C_6H_{12}O_5$

* *Digitalinum verum:* The gitoxigenin in this instance again loses 2 mols. of water, to form digitaligenin, which is the cleavage product actually isolated.

† W. Neumann and Lindner, 1937, state that gitoxigenin is the aglycone of desacetyl-oleandrin, and that of oleandrin is acetyl gitoxigenin.

The *pharmacologic actions* of the genins are identical with those of the glycosides, and are about equally potent. The sugars are inactive in themselves, but they are chiefly responsible for the solubility characteristics, and probably through these they affect the velocity and firmness of the binding in the heart muscle, which is the chief difference between the genins and the whole glycosides. For instance, the effect of digitogenin on the Starling perfused cat heart can be removed by washing; those of digitoxin can not (Straub).

Strophanthus Glycosides.—The various species of Strophanthus (Apocynaceae), which are used by the natives of Africa for the manufacture of arrow poisons, contain several related cardiac glycosides, about which there is considerable confusion. The strophanthin of the U.S.P. and B.P. is the amorphous glycoside obtained from the seeds of Strophanthus Kombé and therefore (from the first letter of the species name) known as "*Strophanthin K.*" Its aglycone is *Strophanthidin.* The crystalline *Gratus (G) Strophanthin* or *Ouabain* is more uniform and is therefore used in research. It is about twice as potent as the official strophanthin. Solutions of either of these deteriorate rapidly and should therefore be prepared fresh.

The unsatisfactory knowledge of the strophanthin glycosides is due partly to incomplete identification of the plants, partly to incomplete isolation of the glycosides; and largely also to conflicting nomenclature: similarly named commercial products may differ widely in potency (Heffter, 1909). The strophanthin originally isolated by Fraser, 1870, was the amorphous Kombé variety (Gilg, 1904).

Strophanthin amorphous (Strophanthin-Boehringer) is the official strophanthin. It occurs in the Kombé, and hispidus. The two are similar, probably identical. Kombé further yields a crystalline strophanthin (Houghton, 1911; Brauns and Closson, 1913, 1914) which is similar. A. Stoll, 1939, reported that three-fourths of the cardiac activity of K-strophanthin is due to K-strophanthosid-beta. The amorphous is slightly more toxic for rabbits than the crystalline Kombé. All three are hydrolyzed by acids with the production of the crystalline *strophanthidin*. This is several times more toxic than strophanthin, and produces similar cardiac action (electrocardiographic, Dresbach, 1938), but with greater tendency to respiratory paralysis (Groeber, 1913). Dresbach and Wadell, 1924, found that the most characteristic effect of strophanthidin consists in emesis, which is also produced by intravenous injection. It is also diuretic; and its peritoneal injection provoked defecation. It is not irritant when applied to the conjunctiva. The *crude drugs* Kombé and hispidus are about equally active.

Ouabain, gratus strophanthin-Thoms; Crystallized Strophanthin-Merck.—This is the only "crystalline strophanthin" on the market. It is the best characterized of the principles. It does not yield strophanthidin. It was first isolated by Arnaud, 1888, from the wood of Acocanthera Ouabaio, and, 1898, from S. glaber. Later, 1910, Thoms obtained it from S. gratus, which was found to be identical with glaber. This is more readily obtained genuine than the other Strophanthus species. Strophanthin has been described as methyl-ouabain, and acocantherin as dimethyl-ouabain; but the evidence for these views is not convincing (Brauns and Closson). Ouabain is about twice as toxic as strophanthin; and this is twice as strong as acocantherin. S. gratus also contains a second amorphous strophanthin (Thoms). The "*pseudo-strophanthins*" of Feist were probably ouabain, but their identity is now obscure.

Cymarin is the active glycoside of *Apocynum* (Canadian Hemp), a plant employed therapeutically like digitalis. Cymarin was isolated and named by Impens, 1913, and investigated by Windaus and Hermann, 1915. It is closely related to strophanthin and yields strophanthidin on hydrolysis. The principles announced by previous investigators (cynotoxin and apocynamarin of Finnemore, 1909, and Moore, 1909; apocynin and apocynein of Schmiedeberg) were probably impure mixtures. Commercial apocynin is acetovanillin (Finnemore, 1908), and is practically inactive (Wood, 1904).

Scillaren.—By special extraction methods to prevent enzymatic decomposition, Stoll isolated a crystalline cardiac glycoside from squills, which he named *scillaren* A. It represents about two-thirds of the total potency of the drug. It yields the aglycone scillaridin. The remainder is constituted by an amorphous fraction, probably impure, which he named scillaren B. The activity of squills was formerly attributed to two amorphous glycosides, scillipicrin and scillitoxin; but Ewins, 1911, found these to be impure mixtures. Kopaczewski, 1914, claimed to have isolated two active principles: scillitin, the toxic constituent, a nitrogen-free glycoside; and scillidiuretin, water soluble, markedly diuretic, but of low toxicity.

Adonis resembles scilla more closely than digitalis (Chevalier, 1913). Roch and Cramer, 1914, found even large doses inefficient in cardiac diseases. Fuckelmann, 1911, claimed that "adonidin" is a mixture of an acid and neutral glycosides, both having digitaloid effects, the acid being also hemolytic. Its cardiac and diuretic actions were investigated by H. Hermann, Jourdan and Ribere, 1930. It has no advantage over digitalis (Hatcher and Haag, 1933).

Convallaria (root of Lily of the Valley); active constituent, the glycoside convallamarin; is considered rather uncertain (Roch and Cramer, 1914).

Helleborein is a glycoside from the rhizome of Helleborus niger (*Hellebore*). Its digitalis action depends on the presence of an acetyl group (Sieburg, 1913). It is not absorbed from the human intestinal tract and therefore produces only diarrhea clinically (Cushny, etc., 1912).

Erythrophleine is an alkaloid with digitalis action, obtained from "Sassy Bark" (chemistry, Power and Salway, 1912), and used by West African natives as emetic, cathartic and ordeal poison (G. W. Harley, 1941). Erythrophleum also contains five other alkaloids. One of these, coumingine, has a stronger cardiac action than erythrophleine; all are more potent in producing emesis, local anesthesia, rise of blood pressure, and stimulation of the uterus and intestines. Cassaine causes convulsions in frogs and cats (Chen, Hargreaves and Winchester, 1938). Cassaine and nor-cassaine produce relatively less cardiac irregularity in heart-lung preparations (H. M. Maling and Krayer, 1946). The erythrophleum alkaloids are esters of mono- and di-methylaminoethanols. *Dimethylaminoethanol* produces positive inotropic effects on the heart-lung preparations of dogs, similar to erythrophleum (A. Farah and Krayer, 1946).

Uzarin is a crystalline cardiac glycoside isolated by Hennig, 1917, from the root of an African plant, Gomphocarpus (Asclepiadaceae), used by the natives against dysentery and other diarrheas (Guerber, 1911, 1920). In addition to the cardiac effects of digitalis, uzarin acts on smooth muscle, small doses being stimulant, and large doses depressant. The stimulation is not inhibited by atropine or epinephrine. It sensitizes the sympathetic system to epinephrine stimulation (Raymond-Hamet, 1928; Gessner, 1930). Uzarin is easily hydrolyzed by acids into glucose and the inactive uzaridine. It is therefore much less effective by stomach than by rectum. *Uzaron* is apurified extract of secret composition.

DIGITALIS ACTIONS ON THE CIRCULATION

Digitalis produces the following important reactions:

(1) *Increased contractility* of the cardiac muscle, *i. e.*, lowered threshold of irritability, and more powerful and more prolonged contraction with corresponding *lengthening of the refractory period*. This entails corresponding changes in the conduction, which is a function of the contractility, *i. e.*, the conduction is *stronger but slower*, also with prolongation and intensification of its refractory phase. This lengthening of refractoriness is the more marked, the shorter the normal refractoriness of the structures. It is therefore most marked in the His bundle, and tends to produce auriculoventricular block.

(2) The *tonus of the heart muscle* is increased so that the *systolic shortening becomes greater and more prolonged.* In the ventricle of the

cold-blooded heart and in the perfused mammalian heart this culminates gradually in systolic arrest. In living mammals systolic arrest is impossible because the heart would be asphyxiated by impairment of the coronary circulation.

The *diastolic tonus* also tends to be increased, and the diastolic relaxation would be less complete. In the intact animal, however, the prolonged refractory condition may lead to a passive distention in diastole, due to the prolonged inflow of blood. This is seen most strikingly in the distended auricles of the digitalized heart of intact frogs. In mammals, the size of the heart is not diminished in diastole, but only in systole (Gold and Cattell, 1939).

(3) *Digitalis stimulates the vagus center* (along with other medullary centers). This is probably due to a reflex from the direct cardiac action, since the vagus action generally appears only after the muscle effects have reached a certain height.

Vagus stimulation diminishes the cardiac tonus and excitability; it weakens the cardiac contractions and therefore shortens the refractory period; the conduction is correspondingly weakened, although it is quickened. All these effects are the opposite of the muscular action of digitalis, and may represent an attempt at a central compensation against the peripheral action. Nevertheless, both actions coincide in interfering with conduction and therefore in tending to produce block, although by opposite mechanisms; the direct muscular action by prolonging the refractory phase, the vagus action by raising the threshold of excitability. Both actions may participate in the therapeutic effect on auricular fibrillation. The muscular action plays probably a rather larger share, for the greater part of the therapeutic effect persists if the vagus action is eliminated by atropine. As the dosage is increased, the vagus phenomena come to predominate; with fatal doses, the muscular action again obtains the upper hand. There is no evidence that the peripheral vagus distribution is stimulated or sensitized by digitalis: the susceptibility to acetylcholine is not increased, but may be abolished even by small doses (J. A. Wells *et al.*, 1943).

(4) Digitalis contracts arterial muscle directly, but this effect plays a relatively unimportant part in its ordinary actions.

The details will be presented in the order of the increasing complexity of the phenomena, *i. e.*, segments of cardiac muscle, perfused cold-blooded heart, excised mammalian heart, intact mammals, and therapeutic effects. In view of the complicated interactions, it is not surprising that results obtained on limited experimental material may sometimes appear contradictory.

Mammalian papillary muscle survives in suitable saline solutions for several hours, and may be stimulated rhythmically. The tension of the twitch is markedly increased by ouabain in very dilute solution (1:100 millions for cats, 1:20 millions for rabbits), especially with fatigued preparations. The diastolic tonus is not increased. With higher concentrations (1:40 millions, for cats) the primary increase is followed by depression (Cattell and Gold, 1938). Camphor, metrazol, coramine and barium do not produce this sustained force (S. Krop, 1944). Ouabain also increases the force and improves the contractile efficiency of depressed *skeletal muscle* (M. K. Cattell, 1942).

Isolated Purkinje Fibers.—The excised His bundle of mammalian heart, when placed in oxygenated Ringer's solution, makes rhythmic contractions like other cardiac muscle, and reacts similarly to pharmacologic agents: it is stimulated by strophanthin, barium, epinephrine, caffeine, calcium and camphor, depressed by quinine, chloroform, potassium and oxalate; vagotropic drugs are ineffective (Pick, 1923; Ishihara and Pick, 1926).

Embryonal Heart of Chick.—The heart of the forty-eight hour chick has not yet developed nerve fibers or a conducting system, but when placed in a 1:300,000 solution of ouabain, it develops A-V block, ventricular arrest, and finally sino-atrial arrest. The time of th- A-V block may be used for bio-assay: It appears cone stantly in four minutes, if the temperature is 39° C.; later, if the temperature or the concentration is lower. The heart revives on washing with Tyrode's solution (G. H. Paff and Johnson, 1938, 1940).

Segments of Frog Ventricle.—Sasaki, 1921, found that helleborein lowers the threshold to stimulation, increases contractility and rhythmicity and the refractory period (*i. e.*, the resistance to tetanus by faradization). Increase of tonus is shown by lengthened duration of the systolic peak and incomplete diastolic relaxation, the duration of the diastole not being increased. This terminates in systolic standstill.

Isolated Auricle of the Frog.—The toxic dose of digitalis is at least ten times as great as for the ventricle: the phenomena, however, are similar (W. Straub, 1915).

Ventricle Segments of Turtle.—Large doses produce acceleration (even after atropine or ergotoxine) and increase of amplitude and tone (Greene *et al.*, 1915). *Tonus waves in turtle auricles* are augmented by vagus stimulation and inhibited by the sympathetic (Rosenzweig); accordingly, they are increased by digitalis (0.3 to 0.5 per cent) and antagonized by epinephrine (Gruber, 1921).

Entire Frog Heart.—The phenomena are identical in perfused hearts, and with the natural circulation. They are preceded by a latent period of five to ten minutes, even if strong solutions are applied directly. Small doses of all digitaloids (Benedicenti, 1902; including barium, Poulson, 1910) produce an *apparently depressant effect, i. e.*, a gradual slowing and diminished tone (F. Williams, 1880, perfused heart), which may terminate in diastolic arrest, especially if the drug is applied to the exterior of the heart (Werschinin, 1910). It is rarely witnessed in intact animals, and is then followed by the usual systolic phase (Boehm, 1872). This depressant effect has been interpreted as vagus stimulation; but it is not prevented by atropine (Benedicenti, 1902), and is probably due to diminished conductivity and heart block (*i. e.*, increased refractoriness) between sinus and auricle, preventing the transmission of the pacemaking impulses (Clark, 1914). The heart still responds to mechanical stimulation. Submaximal vagus stimulation increases the block (Haldschinski, 1908). *If the rhythm is set by extraneous stimulation*, the systole, in its mechanical and electrical manifestations, is shortened by digitoxin; the diastole is lengthened; the refractory period is shortened; the threshold is not materially changed. Conduction is usually slowed (A. M. Wedd *et al.*; 1941).

Therapeutic Stage.—If the digitalis is injected or perfused, instead of being applied to the surface of the heart, the sinus block does not proceed to arrest (Clark, 1912), and the other parts of the heart participate in the effects. The typical course was described by Boehm, 1872. The increase of contractility is shown by increased systolic excursions, which prolong the refractory state, so that the rate is slowed. This offers opportunity for greater filling and therefore for greater diastolic distention. The output per beat is thus increased. The time output and the blood pressure may alter in either direction, according to the degree of slowing. The earlier effects are mainly on the auricles, and the auriculoventricular interval is unchanged (Clark and Mines, 1913). If the heart was weak, the stimulation may also be perceptible on the ventricle (Clark, 1914). Hearts exhausted by perfusion with a saline solution may be revived.

The *toxic irregularities* start soon after. The systolic phase of the ventricle becomes exaggerated, leading to intraventricular block, so that at times the apex, at times the base, remains firmly contracted during the diastole. These partial diastoles may alternate so that the blood is merely pumped back and forth from one part of the ventricle to the other. This has been called, rather inappropriately, "*cardiac peristalsis.*" (The "peristalsis" was first described by Vulpian, 1855). A part of the ventricle may remain firmly contracted for a considerable time, and then may resume rhythmic contraction. Eventually, the ventricular diastoles become weaker, until the ventricle finally goes into permanent *systolic standstill*, and appears as a small white lump, contrasting sharply with the turgid auricles. The apex is often arrested before the base. The auricles continue to pulsate for a time, and eventually stop distended. The ventricular systolic standstill is not paralytic, for if the ventricle is forcibly distended with fluid, it will again start effective beats (Schmiedeberg, 1874). The standstill is due to *excessive tonus*, which prevents diastolic relaxation under the ordinary venous pressure. It is not prolonged contraction, for the heart muscle is not in the refractory phase (Tait and Pringle, 1916). Other hearts may not show the "peristalsis," but instead the phenomena of *partial auriculoventricular "block," i.e.*, the ventricular rate suddenly falls to one-half, then one-third, one-fourth, and so on, of the auricular rate (Straub, 1901). The auriculoventricular interval is lengthened (Clark and Mines, 1913). Eventually the auricular rate, and finally the sinus rate may be halved. The block is explainable by *prolongation of the refractory period*, for Brandenburg, 1904, showed that the heart is now less easily excitable to extrasystoles. K. Junkmann, 1925, reported the refractory period as prolonged by barium and strophanthin, but more complex effects occurred with digitalis. K. Gies, 1927, found the refractory period at first shortened, then lengthened. On the other hand, the *spontaneous contractility* is increased, for if the sinus-auricular junction is crushed (I-Stannius experiment) the ventricles are not arrested as in the normal frog, but at once initiate a spontaneous rhythm. However, A. G. Macleod, 1939, found that the duration of the electrical systole of the auricles and ventricle is reduced and the refractory period shortened. De Noer, 1917, made detailed studies of the effects on existing irregularities, and the like. The *oxygen consumption* of the excised frog heart is decreased according to the diminished rate and excursions (Gottschalk, 1913). Pietrowski, 1917, found that *forcible distention of the auricles* of the normal frog heart produces a systolic tendency and arrest similar to the tonus effect of digitalis. This suggests that clinical auricular distention may potentiate the therapeutic response to digitalis. This tonus effect is not removed by atropine or epinephrine.

The heart of toads is resistant to the digitaloid drugs, so that the action proceeds only to diastolic arrest. It shows a similar peculiarity in its behavior to excess of calcium, which diminishes the tonus of the heart, instead of increasing it as in the frog. Wieland, 1922, suggested that the two phenomena are connected, on the basis of Loewi's interpretation of digitalis action as increased calcium susceptibility. The skin of the toad contains two principles which exert typical digitalis actions.

Perfused Mammalian Heart.—Moderate doses, corresponding to the therapeutic stage, increase the excursions, especially in systole, and slow by prolonging the diastolic pause. The output per beat may be more than double. The *time* required to produce maximal slowing is an hour for digitalis, one-fourth hour for strophanthin (Haynes, 1906). *Existing irregularities are removed*, and fibrillating heart may resume regular contractions (Bodo, 1928). With *toxic doses*, the contractions after the therapeutic stage become quicker and irregular. The diastolic relaxation becomes progressively less complete, and the heart has a systolic tendency. It finally passes through delirium cordis into systolic standstill, the tone increasing even after the heart has stopped. Stretching of the muscle (as by increasing the coronary pressure) may temporarily restore the pulsations (Gottlieb and Magnus, 1903; Etienne, 1909).

The *oxygen consumption* of perfused hearts varies with their rate; it is diminished when they are slowed (J. C. David, 1930, isolated frog heart), and increased when the cardiac activity increases (Rhode and Ogawa, 1912).

Dynamics of Cardiac Digitalis Action.—If the rate of intact dog's heart is kept constant (by auricular stimulation), the direct stimulation of ventricular muscle by digitals and ouabain is manifested as increased gradient of pressure development, higher blood pressure maxima within the ventricles, and quickened rate of systolic contraction. The diastolic excursions are not decreased until toxic effects set in (Wiggers and Stimson, 1926). *Extrasystoles* are produced by smaller stimuli in hearts under the influence of the therapeutic and the smaller toxic doses of digitalis (Pletnew).

Intact Mammals.—The typical phenomena may again be conveniently divided into the therapeutic and toxic stages. During intravenous injection of digitalis, there is a sharp "velocity" fall of blood pressure (Blake). Although this does not last long, it should be borne in mind when contemplating intravenous injections. It does not occur with other methods of administration.

Cardiac changes in the therapeutic stage are characterized by lowering and reversal of the T wave of the electrocardiogram, with relative shortening of the Q–T interval; marked slowing of the pulse, due to lengthening of the diastolic pause; increased diastolic distention of the heart; and more complete systole, if this has previously been incomplete. The heart is therefore both better filled and better emptied (Cushny, 1897). The output per beat is thus greatly increased; the "pulse pressure" or "pulse volume" is improved. This increase more than offsets the slowing, so that the minute output is also increased (Cohn and Levy, 1920). This tends to raise the blood pressure; in animals this tendency is supported by a more or less powerful vasoconstriction, involving particularly the intestines and liver. In man, the blood pressure is not much altered, presumably because of the more efficient vasomotor regulation; nor is the normal human heart usually slowed by ordinary doses, although the conduction of auricular impulses is delayed.

Behavior of the Different Chambers of the Heart.—The two sides of the heart behave very much alike to digitalis; but the auricles tend to show relatively greater inhibitory effects (since they are more subject to vagus control), while the ventricles are more disposed to the muscular action. In the therapeutic stage, the rhythm of the auricles and ventricles is synchronous.

Electrocardiographic Changes.—The reversal of the P and T waves which is characteristic of the therapeutic dosage in man occurs in dogs and cats promptly after the intravenous injection of about 30 per cent of the minimum fatal dose (ranging from 25 to 60 per cent in different cats, but constant in a given individual; Levine, 1919). The reversal occurs after section of the vagi and after atropine, and is therefore a muscular phenomenon (Cohn and Levy, 1918). In normal adults receiving a massive therapeutic oral dose of digitalis, the electrographic changes do not begin till after two hours; they may last for thirty days. About half responded with slowed rate (K. Larsen *et al.*, 1937). The range of sensitivity of the T wave change with oral doses is within 25 per cent in 70 per cent of the population, but 5 per cent differ by more than 50 per cent, occasionally even 300 per cent (H. Gold *et al.*, 1945).

The **digitalis slowing,** in *normal* animals, is practically entirely vagal, due to vasosensory reflexes arising partly from rise of blood pressure, partly by chemical stimulation of the afferent endings of the carotid glomus (Heymans *et al.*) and, perhaps chiefly, by sensitization of the myocardium to vagus stimulation, so that it is inhibited more effectively by rise of blood pressure and by acetylcholine (Abdon *et al.*, 1938). It is almost completely eliminated by section of the vagi (Traube, 1851; Kochmann, 1909); and atropinized animals show practically no slowing. The slowing produced by digitalis in *auricular fibrillation* is a different phenomenon. It occurs even after atropine, and is therefore peripheral (Cushny and Mackenzie; Gottlieb, 1914). It may be explained by the auriculoventricular blocking of some of the supernumerary impulses, through the lengthened refractory phase.

The slowing is due to chemical stimulation, and not merely to rise of blood pressure (as was supposed by A. B. Meyer), for it occurs in the clinical cases in which the blood pressure is unchanged or even diminished (Fraenkel and Schwartz, 1906). In animals the rise of pressure contributes to the slowing, for the slowing is about twice as great if the pressure rises as it is if the pressure is kept just level by hemorrhage (Kochmann, 1906).

With advanced digitalis action, the heightened contractility of the cardiac muscle renders the heart less responsive to inhibitory impulses. Vagus stimulation therefore fails to slow the heart in the later toxic stage (Liagre, 1906), but still weakens the beats. The *duration* of the actual contraction and relaxation are practically unchanged. The *speed* of the systolic contraction is somewhat increased (deHeer, 1912). The slowing occurs mainly in the diastolic pause; the systolic pause is also lengthened a trifle. The *dose required to produce distinct slowing,* on intravenous injection, is from 25 to 70 per cent of the minimum fatal dose (Robinson and Wilson, 1918); *i. e.,* it is about the same as that required to produce the muscular effect, the reversal of the T wave. The different digitalis drugs may differ quantitatively in the degree of vagus stimulation (Etienne, 1909).

The cardiac output per beat as well as per time depends on the venous return, and in pathologic hearts also on the improvement of the cardiac condition. In *normal man,* Burwell *et al.,* 1927, found the output actually diminished by 1.4 to 2.7 Gm. of digitalis, due to diminished *venous return* (Rytand, 1933). S. Weiss and Blumgart, 1929, found the *pulmonary blood flow* unaffected by large therapeutic doses in normal individuals, but increased by an average of 30 per cent in decompensated heart disease. In *dogs,* Cushny, 1897, estimated the output per beat as increased up to 50 per cent; the output per time to 20 per cent. Tigerstedt, 1907, also showed with the stromuhr that the output is generally increased. Heinz, 1900, found the flow of blood from the carotid, at a constant pressure, increased by 50 to 250 per cent. The *circulation time* is shortened in the pulmonary and in the general circulation (Langlois and Desbouis, 1915). The *vein pressure* is not materially altered, even when the arterial pressure rises (Capps and Matthews, 1913).

Blood Pressure.—In most animals (but not in man), there is marked and sustained rise of blood pressure during the therapeutic and toxic stage, except when the vagus slowing or the irregularities become excessive. The rise is due partly to the increased output of the heart, but mainly to the direct constrictor action on the arterioles, especially in the intestines.

The increased output of the heart should result in a rise of pressure. Accordingly, the pressure rises even when changes in the peripheral vessels are definitely excluded (*f. i.*, in Bock's method, where the aorta is tied, the circulation being shunted through the carotid directly to the jugular vein—Bock, 1898; C. W. Greene, 1910). While the digitalis heart can discharge a larger volume of blood against a normal pressure, the *maximal pressure*—*i. e.*, the rise of pressure on clamping the aorta—is not increased (Heinz, 1900).

Vasoconstriction.—The predominant share of this in the rise of pressure is shown by the decreased volume of the important splanchnic organs as the blood pressure rises (Gottlieb and Magnus, 1901). Further evidence is that the venous outflow is also decreased, and that the rise is not always accompanied by increased output of the heart (Tigerstedt, 1907, stromuhr). These experiments however, were made with doses far larger than are used in therapeutics. Small therapeutic doses may produce intestinal constriction even when the blood pressure does not rise. The vascular effects are more lasting than the cardiac (Joseph, 1913). The *vasoconstrictor effect is peripheral* because *it occurs in excised organs* (Brunton and Tunnicliffe, 1896). The action is presumably exerted directly on the arterial muscle. Strophanthus produces moderate stimulation of the *vasomotor center;* digitalis much less or none. The central action is not sufficient to make itself felt through the other actions of the drugs. Fatal doses result in sudden cardiac arrest and asphyxia, thereby producing intense stimulation of the vasomotor center (Pilcher and Sollmann, 1915). Very dilute solutions of digitalis produce dilatation of perfused vessels (Fahrenkamp, 1911).

Differences in Digitaloids.—The data are inadequate for definite conclusions; deHeer, 1912, and Joseph, 1913, found that ouabain had a strong constrictor effect in mammals; while Moog, 1912, claimed that its constrictor action is but one-tenth that of digitoxin. Stroomann, 1914, found strophanthin the weakest constrictor in frogs. Caffeine is antagonistic. Vogt, 1909, claimed that strophanthin does not produce constriction in *man*, but Straub, 1909, brought evidence of constriction with the string galvanometer.

Blood Pressure in Rabbits.—These do not show so great or constant a rise as do other animals; but if the pressure has been lowered by hemorrhage, digitalis produces an effective rise toward the normal level (Hernando, 1911). Digitalis did not produce much rise after chloral, presumably because the heart was too greatly injured.

Differences in Vascular Areas.—The constriction is strongest in the intestinal and splenic vessels, less in the renal, and weak in the vessels of the skin and brain. The *blood flow* is decreased in the intestines and muscle, increased in the kidneys by therapeutic doses, slightly increased in the brain. The coronary flow follows the cardiac output; it is decreased for normal hearts, increased for damaged hearts (F. Hildebrand, 1941, thermostromuhr, anesthetized dogs). Toxic doses constrict the renal vessels.

In the *kidneys*, the dilatation is partly direct, for with excised organs certain concentrations dilate the renal vessels, while they constrict the intestinal vessels. However, in eviscerated rabbits with automatic blood pressure compensation, digitalis produced renal constriction (Ogaki, 1927). *Pulmonary vessels* are somewhat constricted in perfusion experiments (Tschistowitch). Excised arterial rings are also constricted by all digitaloids, except digitonin, which dilates (Macht, 1914). In life this action is unimportant; for the slight rise of pressure in the pulmonary artery is mainly cardiac (Plumier, 1905; Wiggers, 1911). The filling of the *vessels of the pia mater and retina* follows the general blood pressure (Hirschfelder, 1915).

Coronary vessels may be constricted, especially by digitoxin, less by strophanthin (Rabe, 1912). Excised arterial rings are also constricted (Voegtlin and Macht, 1913). The constriction would be overcome by the improved cardiac contraction; so that the *coronary flow in life* was found unaltered by therapeutic doses (Bond, 1911), or even increased (Sakai and Saneyoshi, 1915). Essex *et al.*, 1938, found no significant change in the coronary flow in the dog after nine days of digitalization; but continued toxic doses may decrease it (W. H. Dearing, Essex *et al.*, 1943). J. L. Miller, 1908, found that digitalis enabled the heart to tolerate a greater degree of *coronary obstruction*, but Kisch and Schwarz, 1936, did not obtain improvement of the anemic changes in the electrocardiograms, in rabbits. Large toxic doses contract the coronary vessels even in life, with rising blood pressure; this is sometimes followed by increased flow with falling pressure (Sakai and Saneyoshi, 1915).

Thoracic Lymph Flow.—In normal animals, this is not changed during the rise of arterial pressure; nor is the pressure in the portal capillaries increased (Yanagawa, 1916).

Toxic Effects on the Circulation in Mammals.—These are characterized by irregularities of the rhythm and strength of the cardiac pulsations. They are exaggerated manifestations of the vagus and cardiac stimulations which were initiated in the therapeutic stage. The *vagus effects* (slowed rhythm, diastolic tendency, lessened conductivity) reach their acme most rapidly; so that the first indications of overdosage are commonly those of marked inhibition. This inhibition is in turn overcome as the *muscular excitability* becomes greater and greater; thus the final effects are mainly muscular (increased tone, heightened irritability, spontaneous ventricular rhythm, extrasystoles). The irregularities which result from these interactions weaken the circulation and interfere with the nutrition of the heart, until this becomes arrested. Cushny, 1897, divided the successive effects into the inhibitory stage and the stage of muscular irregularity. *In the typical course,* the effects pass successively through the therapeutic, vagus and muscular stages; but the vagus stage is often omitted in animals. The "toxic effects" in man are generally of the inhibitory type.

The **inhibitory stage** corresponds to strong vagus stimulation. The rhythm becomes very much slowed—to 40 or 50 beats per minute. It is often irregular; there are scattered diastolic pauses which become more frequent and lasting, particularly in the auricles. These irregularities are partly exaggerations of the normal respiratory variations, but they are often independent. The two sides of the heart contract at the same rate, but the ventricles are likely to assume a spontaneous rhythm, which may be faster or slower than that of the auricles. This independent rhythm is due to the blocking of the auricular impulses by the lessened conductivity. The excessive slowing and the irregularity diminish the time output of the heart in this stage, although the amplitude is increased. The blood pressure falls.

In the stage of muscular irregularity, the rate, rather suddenly, becomes more and more accelerated, as if the heart escaped from the vagus influence. Electric vagus stimulation has less and less effect on the rate; but since it still increases the diastole the vagus cannot be paralyzed. The escape is due to the excitability of the heart becoming so greatly increased that the vagus is unable to restrain it. The auricles and ventricles may at first keep the same rate; but the ventricles soon assume a rapid rhythm independent of that of the auricles; for the conduction of the auricular impulses is more and more blocked, while the spontaneous excitability of the myocardium is more and more increased. The accelerators usually do not respond to stimulation (Fredericq, 1913).

This independence of the auricular and ventricular contractions results in curious *periodic variations* in the volume of the pulse, the rhythm at this time being fairly regular. One or more enormously strong beats are followed by much weaker beats, sometimes quite imperceptible in the pulse, which is therefore *intermittent.* These phenomena recur in groups, which remain fairly regular for a short time, but soon change to some other type. These effects are sometimes due to respiration; in other cases they are cardiac. These are also seen in the atropinized heart, and are mainly due to the *arrhythmia of the auricles and ventricles* (Cushny, 1899). As a consequence, the contractions will sometimes alternate, sometimes coincide, forming groups. If the auricular systole occurs during the ventricular diastole, the ventricles will be filled with blood when they contract, and the result will be a large pulse wave; if the auricular and ventricular systoles coincide, no blood will be moved, and there will be no pulse The two sides of the heart continue to beat synchronously, although the periodic variations of strength have no relation. After a time, *extrasystoles* (*i. e.,* premature contractions by which no blood is expelled) appear, and the pulse shows corresponding intermissions. These become more numerous. The rate continues to increase, becoming faster than in atropine poisoning. Various complex irregularities are superadded, and the contractions become thoroughly disorganized.

Terminal Changes.—The quickening of the rate soon exceeds the optimal limits. The contractions become superficial, fluttering, much less effective, and more fatiguing. The blood pressure falls and the heart is unable to keep the pace. First the auricles, then the ventricles, pass into fibrillation and the circulation is arrested. The chambers stop in median position, and then gradually become greatly dilated.

Racial Tolerance.—Great differences exist in the susceptibility of different species to digitalis poisons. Rodents, toads (Vulpian, 1856) and the grass snake are especially resistant, but not immune. The *resistance of the toad and snake* does not extend to the related action of barium or saponin (Clark, 1913). The toad resistance is generally attributed to habituation for its own poison; and Filippi, 1913, claimed that toads deprived of their poison are sensitive to digitalis. The fatal dose for *rats* is nearly a thousand times greater (per kilogram) than that for cats, even hypodermically (Hatcher, 1909), and thirty times as much as for rabbits. Gunn, 1913, found that the concentration required to arrest the isolated heart in a given time is also forty times greater for rats than for rabbits, showing that the difference lies chiefly in the heart itself. Excised papillary muscle of *rabbits* is considerably less susceptible than that of cats to minimal doses of ouabain (Cattell and Gold, 1938). Rabbits also *excrete digitaloid glycosides more rapidly* (Hatcher, 1912). Salvisberg, 1907, claimed that ruminants are more resistant to oral administration, but not to intravenous, indicating that in these animals the drugs are partly destroyed in the digestive canal. Lhota, 1909, stated that young animals are more resistant than adults. *Pigeons* tolerate intravenously twenty-five times as much digitalis (per unit of body weight) as do cats, but only about twice as much ouabain or strophanthin. However, many of the pigeons injected with 75 per cent of the acute M.F.D. of digitalis die somewhat later; especially with digitoxin (Haag, 1936). *Seasonal variations in susceptibility* occur in frogs and guinea pigs. They run reverse to the seasonal variations of acetonitrile and diphtheria toxin (Haskell, 1914).

Influence of Various Conditions on Digitaloid Effects.—The response to digitalis is influenced not only by its concentration, but also by other conditions, especially by pathologic changes in the heart which will be discussed in the therapeutic actions; and also by temperature and by the chemical agents. The effects of the latter may be somewhat different with intact animals from those with excised hearts. The *additive effects* of *calcium* are of practical importance, because of the danger in the simultaneous use of these drugs. Intravenous injection of calcium in mammals is generally believed to render these materially more susceptible to the toxic cardiac effects of the digitaloid drugs (Gold and Edwards, 1927). The subject is in dispute.

Contrary results of Nahum and Hoff, 1937, are criticised by Gold and Kwit, 1937; but P. K. Smith, Winkler and Hoff, 1939, reported a further series of intravenous injections of dogs which failed to show that the fatal dose of calcium is smaller in digitalized animals, or that digitalis renders the heart more susceptible to calcium fibrillation, or that calcium increases the toxicity of digitalis. They attributed the potentiation reported by others to the variable toxicity of calcium and digitalis. The toxicity of digitalis is also increased (by 20 to 30 per cent in cats) by the rapid intravenous injection of *hypertonic solutions* of sodium chloride, dextrose or urea, and by theophylline or theobromine. It is decreased by caffeine. Mercurial nephritis and ligation of the ureters increase the toxicity (R. Kohn and Costo-Panageotis, 1933). Strophanthin action on isolated frog heart is intensified by adding urea, presumably through increased adsorption on the surface (Heim, 1939). *Hyperpyrexia* (by hot baths) increases considerably the toxicity of digitalis for intact mammals; the effects, including the reversal of the T wave, are qualitative as in normal mammals (Hirschfelder *et al.*, 1920). *Beriberi* patients are said to be resistant to digitalis. Beriberi pigeons are reported to be more resistant to both the cardiac and emetic actions of digitalis, but more susceptible to strophanthin (Mehes and Peter, 1934).

Influence of Conditions on the Digitalis Response of Excised or Perfused Hearts.—Sollmann, Mendenhall and Stingel, 1915, determined the *ratio of concentration and activity.* The feebler the actions of ouabain, the more is its activity increased by doubling the concentration. Holste, 1912, and Weizsaecker, 1913, found that the *vigor of the heart* influences the response quantitatively. The greater the intensity of the cardiac functions, the prompter the strophanthin effect. The cardiac effects of the digitaloids on frogs increase with the *temperature* (Trendelenburg, 1909), the increase being greater for low than for high temperatures. The activity is increased by heat, not only directly, but also through the more rapid heart rate (Sollmann, Mendenhall and Stingel, 1915). In the perfused mammalian heart, the effects are also quickened by heat; in this case the more rapid coronary flow is a contributing factor (Gunn, 1914). Werschinin found the systolic action much weaker in Ringer's solution than in *serum* solutions of the drugs. Oppenheimer, 1913, observed that serum inhibits the action of the less soluble digitaloids, but not of strophanthin. Cholesterol and egg albumen did not have equivalent effects. *Oxygen* increases the digitalis effect (Gruenwald, 1912).

Influence of Ions.—The systolic digitalis action occurs only if the perfused solution contains *calcium ions* Excess of alkali or absence of potassium rather increases the systolic action; excess of Ca has little effect (Clark, 1912). On the other hand, strophanthin delays the standstill of the heart when this is perfused with Ca-free solutions or with pure K solutions; but it hastens the arrest when added to a solution from which Ca and K are both absent (O. Loewi, 1912; Konschegg, 1913). Strophanthin may therefore to a certain extent replace Ca, and thereby antagonize the K ions. The effects of the ions on the vagus action are quite different (Clark, 1914). Addition of decalcifying agents restores the beat of embryonic chick hearts when this has been arrested by digitalis (Paff, 1940). The potency of digitalis glycosides for embryonic chick hearts is inversely proportional to the *potassium* ion content of the medium (R. A. Lehman and Paff, 1943). Oral administration of potassium chloride (5 to 10 Gm. for man) abolishes ectopic beats resulting from digitalis (J. J. Sampson *et al.*, 1943). Therapeutic doses of digitalis in cats produce a significant increase of the potassium and water within the cardiac muscle cells, and decrease their chloride (P. K. Boyer and Pointdexter, 1940).

Hypertonic Solutions.—Gramenitzky, 1937, reported that if a heart which has been arrested by digitalis is transferred to Ringer's solution rendered hypertonic by the addition of 1½ to 2 per cent of sodium chloride, the auricle is immediately revived.

Antagonism with Alkaloids.—A perfused frog heart that has been slowed and weakened by the vagus action of pilocarpine is strengthened but not quickened by digitalis (Ransom, 1917). Lhota, 1909, claimed that cocaine diminishes the toxicity of strophanthin by lessening the cardiac excitability. Wilbur, 1911, found that strychnine often removed the ouabain heart block in terrapin's heart. He reported that *irritants* (iodine) produce effects similar to those of digitalis on terrapin's heart. *Procaine, quinidine, 883F and 933F,* which inhibit ventricular fibrillation from epinephrine, are not effective against that of digitalis (G. A. Emerson, 1943).

Blood Coagulation.—Digitalis glycosides have a thromboplastic effect *in vitro,* and intravenous toxic doses shorten the coagulation time. Heparin lowers the toxicity (S. C. Werch, 1943; D. I. Macht, 1943). Massie *et al.*, 1944, report that coagulability increases during long-continued clinical digitalis therapy. N. C. Gilbert *et al.*, 1944, suggests that this is responsible for the incidence of thrombosis in digitalized patients. Others, however, failed to demonstrate a significant change of coagulability with oral digitalis therapy of patients (Sokoloff and Ferrer, 1945) or on dogs (J. A. Richardson and Walton, 1946).

Central Effects of Digitalis.—The peripheral effects dominate the symptom-complex so greatly that the direct central effects appear unimportant. The cardiac action is so selective that frogs whose hearts have been stopped by digitalis may hop about as if normal. The *medullary* centers are probably stimulated directly, but the indirect effects from the altered circulation are much more important than any direct actions.

Central Symptoms.—When digitalis is injected into the ear vein of *unanesthetized* rabbits, or subdurally, symptoms occur immediately and appear to be largely central. They consist in dyspnea; tremors and convulsions; miosis; debility and paralysis of certain muscle groups, especially the neck; abolition of certain reflexes. These effects are followed by asphyxial convulsions with mydriasis and death by paralysis of the respiration or heart. The later symptoms are, at least partly, due to the circulatory changes; but the earlier symptoms are probably due to direct central actions (Santesson and Strindberg, 1916).

Direct application of strophanthin to the cerebral motor cortex produces clonus and generalized convulsions (as do also nicotine and caffeine; Rizzolo, 1929).

Respiration.—Hypodermic or intravenous injection produces a primary increase of the respiration in rabbits. Larger doses depress (Gross, 1914). *Excised bronchial muscle* is not affected by strophanthin (Trendelenburg, 1912).

The **gallbladder** is stimulated (Lieb and McWhorter, 1915).

Uterus.—Strophanthin revives the movements of the excised uterus when these have been arrested by calcium-free Ringer's solution. Short exposures to strophanthin render the uterus hypersensitive to calcium (Ransom, 1920).

Skeletal Muscle.—If a frog's sartorius muscle is immersed in dilute ouabain solution (1:1,000,000) and then suspended in air, it reacts to stimulation with gradually increasing twitch tension and increasing heat production. This is followed by abrupt diminution of both functions and finally complete loss of excitability. Rapid recovery occurs on immersion in Ringer's solution, even that containing the ouabain; nor do the toxic effects develop while the muscle is kept immersed in ouabain-Ringer solution (Cattell, 1938). The effects resemble those of potassium, and the changes are consistent with the assumption of escape of *potassium* from the muscle cell, which has been demonstrated for striated frog muscle and for the tissues of dog's heart-lung preparation (M. K. Cattell, 1943).

H. Freund, 1936, reported that the effects of digitaloids on the metabolism of skeletal and cardiac muscle are similar; therapeutic doses increase the formation of lactic acid from glycogen, with the opposite effect from toxic doses. Skeletal muscles take up active quantities of strophanthin from the circulation.

The **chromatophores** of toad skin are contracted by cardiac glycosides with the minimal concentrations that cause systolic arrest of the heart (Hargreaves *et al.*, 1938).

The epinephrine output is not affected by strophanthin (Stewart and Rogoff, 1919). Previous workers used inadequate methods.

Local Actions.—Digitalis and the allied drugs, when injected hypodermically, cause fairly severe irritation, pain and abscess formation, which practically preclude their use by this channel. Intramuscular injection is feasible, although not painless. Cardiac glycosides lack *carcinogenic action* when tested on mice (P. K. Smith and Gardner, 1939).

Relative Irritant Action.—Holste, 1913, from hypodermic and conjunctival application to rabbits, established a series for the isolated principles as: most irritant = digitoxin; then digitonin, then digitalein and cymarin (from apocynum). Practically nonirritant = digitalin, ouabain and strophanthin. Digalen was much more irritant than digipuratum. On the skin of young pigs, O. Loeb and Loewe, 1916, also found digitoxin and digalen the most irritant. Digipuratum, strophanthin and ouabain were about as irritant as digitalis infusion. Strophanthin does not inhibit the *emigrations of leukocytes* from inflamed mesentery (Ikeda, 1916). Steinach, 1888, and Panas, 1890, found that application of strophanthin to rabbit's conjunctiva produces *local anesthesia* lasting several hours. In man, however, there is considerable inflammation. Other digitaloids are also anesthetic.

THERAPEUTIC USE OF DIGITALIS

Historical.—The professional use of digitalis is relatively recent. It was recognized by William Withering of Birmingham (Cushny, 1915) as an ingredient of an old woman's secret formula. After ten years of experimentation, he published his results in 1785. He was chiefly interested in the diuretic effect, and mentions the cardiac action only incidentally. The evidence for the connection of the circulatory and diuretic effect was first emphasized by John Ferriar in 1799. The drug quickly assumed an important place, though its proper field was not recognized. The cardiac slowing particularly attracted attention, and as late as 1851 Traube referred the clinical effects entirely to this "depressant" action; hence, digitalis was used in aneurysm, internal hemorrhage, and the like, for which it would be entirely unsuitable. Ten years later, Traube accepted the rise of blood pressure, which had been discovered in animals, as the basis of the therapeutic effect. *Strophanthus* was brought to Europe in the early sixties, and its cardiac actions were promptly discovered. Its introduction into medicine is due mainly to Th. R. Fraser, 1885. The use of *Scilla* dates from the ancient Greeks, although its cardiac action was not recognized. *Apocynum* was used by the early settlers as a hydragogue cathartic and diuretic; presumably they learned of its use from the Indians. *Convallaria* has also been used for several centuries in domestic medicine, against cardiac symptoms.

Clinical Field.—Digitalis and the allied drugs are especially useful to secure and maintain compensation in chronic cardiac diseases, when the heart contracts imperfectly and becomes dilated; either because of incoordinated or irregular contractions, as in auricular fibrillation, or because of exhaustion of the cardiac muscle by its inability to compensate for the mechanical defects of structural lesions. The indications for its employment are governed by the functional conditions of the cardiac muscle, and only indirectly and to a minor degree by the gross anatomic lesions. The most striking results are seen in auricular fibrillation; but definite though less obvious improvement occurs in chronic dilatation with normal rhythm. In this case, the improvement tends to be self-perpetuating, so that digitalis needs to be given only at intervals. With auricular fibrillation, the effect must generally be maintained by more or less continuous administration. Digitalis medication has not given definite clinical results in acute cardiac conditions, other than exacerbations of chronic lesions; partly perhaps because it was administered by methods in which its action is developed too slowly to meet acute conditions; but mainly because acute heart failure is generally due either to profound intoxication of the cardiac muscle, or is secondary to other conditions (for instance, vascular paralysis in fevers, and so forth), which must be the real object of treatment.

Explanation of Clinical Effects.—The slowed conduction and the muscular stimulation are both important; the slowed conduction is the more important in auricular fibrillation; the muscular stimulation in uncomplicated dilatation. The improved tone and contractibility of the muscle increases the amplitude of the systolic contraction, and thus the time output. It counteracts the dilatation directly, and may narrow a leaking valvular ring. In auricular fibrillation the slowed conduction is especially important. This blocks the majority of the confusing impulses and permits the ventricle to make effective contractions. All these actions increase the efficiency of the circulation, insuring a better filling of the arteries, improving nutrition and oxygenation, and relieving the congested veins. The heart is among the first to feel the effects of this improvement. The vicious circle of weaker heart, poorer circulation is reversed into the beneficial stronger heart, improved circulation; so that the effects outlast the administration of the drug, and the improvement is perpetuated. At the same time, the circulation in the kidneys is improved by the faster blood flow, the increase of pulse pressure and the relief of the venous pressure. The kidneys are thus placed in the best condition for filtration or secretion. The anuria is relieved. If there has been edema, the improved kidney action results in extensive diuresis and thus in the absorption of the edematous fluid. This in turn improves the heart action and the whole circulation, by relieving them of the compression of the ascites. The vasoconstrictor action may also play some part; since it is strongest in the intestines and liver, it may help to relieve the congestion of these organs. Rise of blood pressure, as such, has no important share in the action, for it rarely occurs clinically, even with intravenous injection, or in cases which are greatly benefited (Fraenkel and Schwartz, 1907).

Recapitulation of the Effects of Clinical Doses of Digitalis on Normal Man.—The most constant and definite change is the *reversal of the T wave of the electrocardiogram* (Cohn, 1915). It is ascribed to the increased muscular irritability. Diminution of the wave is distinct in about ten hours, with relatively small doses ($\frac{1}{4}$ minim of the standard tincture per pound bodyweight); this may serve for a physiologic assay. With the intensive dosage (1 minim per pound, at one dose), the effect is visible in two hours and reaches its maximum in eight or nine hours (Pardee, 1923). *Auriculoventricular conduction in man* is always impaired, being an early and positive sign of digitalis action. It may be observed within forty-eight hours, and increases with the administration, from simple lengthening to heart-block. After withdrawal, it persists generally about two days, but sometimes two weeks. Full therapeutic doses (a total of about 25 cc. of the tincture) are required to produce a definite lengthening of the auriculoventricular interval. The effect is largely vagal, for it is generally removed by atropine (White and Sattler, 1916).

Heart Rate in Man.—Patients with auricular fibrillation, or with adynamic or unstable hearts, respond by slowed pulse to ordinary doses; but the rate of the normally rhythmic heart, whether the rate be fast or slow or normal, is generally slowed only moderately, and only by doses that produce toxic effects (0.4 Gm. per day for five to seven days). Some patients, especially children, may react to smaller doses. Slowing of the rhythmic heart is therefore generally a toxic rather than a therapeutic phenomenon. It is partly but not entirely vagal, for in many patients it cannot be completely removed by atropine (Wedd, 1919).

Blood Pressure in Man.—The rise of pressure which is characteristic for most animals is not often seen in man, either in health or disease (Czylharz, 1900; Schwartz, 1906; Cushny, 1911; Mackenzie, 1911; Price, 1913; Cohn, 1915; Eggleston, 1917). In heart disease, the improvement under digitalis may even be accompanied by a fall of pressure, if this has been abnormally high (Fraenkel, 1905; Price, 1914; Martinet, 1914). A rise is exceptional, occurring only if the pressure has been below the normal level. The diastolic pressure is always lowered when digitalis relieves uncompensated lesions, no matter what the changes in the systolic pressure. The pulse pressure is therefore generally increased (Martinet, 1914).

The difference cannot be explained by dosage, for in animals the rise occurs with the smallest doses which have a noticeable effect on the heart. It is explained by the more perfect blood pressure regulation of man, which compensates the pressor tendency by inhibition of the vasomotor center and by stimulation of the vagus center. If the digitalis slowing is prevented by atropine, the pressure rises also in the human subject (Fraenkel, 1905).

Digitalis in Auricular Fibrillation.—This condition, which constitutes a half of all cardiac irregularities (Lewis), and two-thirds of all serious cardiac failures (Mackenzie), shows the most striking improvement under digitalis (Cushny, 1911; Mackenzie, 1911). The effect on the auricles themselves is relatively slight; the auricular tone should be increased, and the auricular distention would be relieved by the improved circulation; but the multiple irregularity of the fibrillating auricle is not notably altered, even under continued digitalization. The fixed circuit of auricular flutter (Lewis, Feil and Stroud, 1920) is often broken up by the increase of the refractory phase, under digitalis, and is temporarily split up, as it were, into multiple circuits, *i. e.*, fibrillation (Lewis, 1911); and with further increase of refractoriness, these temporary paths may also be blocked and a regular rhythm attained (review, Garrey, 1924).

The main improvement, however, is in the ventricular contractions. These do not become regular, but the irregularity is decreased, and the rate is reduced from 120–160 to 80–100. The ventricular efficiency, which was greatly impaired by the disorganized rhythm, is much improved, and with it the cardiac output and the blood flow (G. N. Stewart and Scott, 1915). The dyspnea and all the other symptoms of cardiac insufficiency are relieved, including the exaggerated acceleration of physical exercise (W. Modell *et al.*, 1941). The slowing and regularization of the ventricles is due mainly to decreased auriculoventricular conduction, which blocks many of the excessive auricular impulses from the ventricle (Cushny, 1917; 1918), so that the ventricles respond more forcibly and more effectively to the remaining impulses. The block is effected by the summation of vagus stimulation, which tends to predominate with moderate doses; and a myocardial factor, the increased refractoriness that follows stronger contraction of the bundle, which is involved especially with full doses. Atropine, 2 mg. intravenously in man, which eliminates the vagus factor, usually prevents slowing by conservative digitalis dosage (Cushny *et al.*, 1912), but not with intensive digitalization (Gold, Kwitt *et al.*, 1939).

A third mechanism of blockage is illustrated by quinidine, which increases refractoriness directly, *i. e.*, by checking the restorative metabolism. The effects of the three measures are contrasted in the table. It may be added that overdosage with digitalis (also with barium, aconite, etc.) may produce auricular fibrillation (Cushny, 1911), by causing intra-auricular blocks that interfere with the orderly progress of the excitation wave. This is especially likely to occur with intravenous injections if the myocardium was severely damaged, and in coronary occlusion (Robinson *et al.*, 1924).

To obtain the best results in auricular fibrillation, the digitalis must be started with full doses. Smaller doses must then be continued for a long time, giving just enough to keep the rate between 70 and 80 per minute. Overdosage is often indicated by occasional reduplication of the pulse ("coupled beats," "pulsus bigeminus"), due to ventricular extrasystoles (Lewis, 1911). Although this may occur with relatively small doses, it is considered an indication to reduce or to discontinue the digitalis. If the auricular fibrillation occurs in cardiosclerosis or when the myocardium is excessively weakened, digitalis is much less effective and much more dangerous.

Influence of Cardiac Irregularities on Cardiac Output.—Experiments on dogs show that *extrasystoles* have little effect, even when they are frequent (1 in 4 to 8). *Auricular flutter* and especially *auricular fibrillation* reduce the output considerably. This is due to the irregularity (premature beats and the like) rather than to the rapid rate. *Heart block,* partial or complete, diminishes the output greatly, proportional to the slowing (Eyster and Swarthout, 1920). Cardiac insufficiency generally increases the *oxygen consumption of the heart,* especially in relation to the output. This uneconomical oxygen use decreases with the first sign of improvement (Gremels, 1933).

Other Arrhythmias.—Irregularities other than those arising from auricular fibrillation and flutter are not materially improved by digitalization, and this is contraindicated in partial heart block. It must not be forgotten that over-dosage of digitalis may provoke any of the clinical types of irregularity even in a healthy heart, and this may occur more readily when the heart is disposed to them by disease. It is therefore necessary to watch carefully for the appearance of any irregularities.

Partial Heart Block (diminished conductivity of the auriculoventricular bundle).—This is always exaggerated by digitalis: a slight retardation between the auricular and ventricular contractions may thus be converted into a partial block, so that the ventricles respond only to every second or third beat of the auricles; or a partial block of this kind may be converted into a complete block, the ventricles assuming their characteristic slow independent rhythm. In partial heart block (even when the a-c interval in the jugular tracing is merely lengthened) digitalis should be avoided, and employed only with caution when it is otherwise urgently needed. If the need for it exists, however, it may relieve the symptoms even though it exaggerates the partial block.

TABLE OF CONTRAST OF CARDIAC ACTION

Function		Digitalis	Vagus Stimulation	Quinidine
Tonus		Increased	Decreased	Decreased
Contractions		Stronger	Weaker	Weaker
Refractory phase		Longer	Shorter	Longer
Conduction		Stronger but slower	Faster but weaker	Slow and weak
Partial heart block		Exaggerated by long refractory pause	Exaggerated by weak conduction	Probably exaggerated by long refractory pause and poor conduction
Auricular Fibrillation	Aur. rate	May be decreased by lengthened refractory or increased by heightened irritability	Increased by shortened refractory period	Decreased by lengthened refractory per. and diminished excitability
	Ventr. rate	Slowed by lengthened refract. per. of bundle	Slowed by weak conduction in bundle	Slowed by lengthened refract. per. and diminished excitability of bundle and muscle

Complete Heart Block.—In this, digitalis can do no further harm, for it does not slow the spontaneous ventricular rhythm. On the contrary, it would tend to quicken the beat; at all events it would tend to render it more effective. It might therefore be of some use (Bachmann).

In complete experimental heart block (dogs) strophanthin first increased the rate and strength of the ventricular contraction. This was followed by sudden ventricular arrhythmia and tachycardia, increasing to fibrillation. The auricles were strengthened, their rate sometimes quickened or slowed. The blood pressure rose in the first, and still more in the second stage (van Egmond, 1913).

Irregularities in the Strength of the Cardiac Contractions (Pulsus alternans).—These are attributed to exhaustion of the myocardium. They are therefore improved by digitalis (Windle, 1917; Christian, 1915). It must be employed with caution, for similar irregularities are prominent in digitalis poisoning, and an exhausted heart is more subject to these effects.

Extrasystoles are not removed by digitalis since they are probably due to heightened irritability of the myocardium—a condition which could only be exaggerated by digitalis. Extrasystoles due to nervous exhaustion, indigestion, nicotine, and so forth, do not require medicinal treatment; they tend to disappear under suitable hygiene, and in any case they have no serious significance. (The influence of various drugs on extrasystoles was studied by McCord, 1912). Guthrie, 1917, reported that digitalis (toxic doses) decreases the irritability of frog and turtle heart to extrasystoles by electric stimulation.

Periodic changes in sinus rhythm (such as the exaggerated respiratory variations, which occur in general nervous exhaustion, rather than in cardiac disease) are not benefited by digitalis. On the contrary, the vagus stimulation would tend to render them more marked.

Paroxysmal Tachycardia.—The response varies. In some cases, digitalis is practically ineffective; in others, intravenous strophanthin reduces the rate strikingly.

Febrile Tachycardia.—The heart rate in fever is not materially affected by digitalization, although the reversal of the T wave and the effect on auricular fibrillation are produced in fever just as with normal temperature (Cohn and Jamieson, 1917).

Irritable Heart.—The simple tachycardia of the "effort syndrome" is not slowed by digitalization (J. Parkinson, 1917), nor is that of Basedow's disease (Cohn, 1915).

Myocardial Insufficiency with Normal Rhythm.—In functional impairment of the efficiency of the cardiac muscles, without changes of rhythm and without lesions of the valves, digitalis does not usually slow the heart rate even when this is fast; but it increases the excursions (roentgen observations, A. E. Cohn and Stewart, 1924), and causes the disappearance of the symptoms, including the edema (Cushny, 1911). This may be attributed to the direct muscular stimulation. If the cardiac muscle is degenerated, as in cardiosclerosis, digitalis will be useless or even harmful, by imposing too great a task on the few weakened muscle fibers remaining.

Use of Digitalis in the Special Cardiac Lesions.—No cardiac lesion, as such, either indicates or contraindicates digitalis. Whatever the lesion, digitalis would be superfluous so long as compensation is fairly perfect. The indications for its use arise only when compensation fails; then its possibilities for good or harm are determined by the functional conditions, and not by the location of the anatomic changes.

Mitral Stenosis.—It has been suggested that the lengthened auriculoventricular pause would permit a better emptying of the auricle (Cohn and Fraser, 1913).

Aortic Insufficiency Not a Contraindication.—The older clinicians, since Corrigan, considered digitalis contraindicated in this condition, fearing that the prolonged diastole would give the blood in the brain a chance to gravitate back into the heart, and thus produce syncope. Although this explanation may be questioned, acute or chronic surgical injury to the aortic valves in animals increases their sensitiveness to digitalis, by as much as a fourth (A. E. Cohn and Stewart, 1928; Weese and Dieckhoff, 1934). However, the clinical use of digitalis in this condition is not unduly dangerous (Christian, 1919) and it is now given freely, as in other lesions. It is advisable to keep the patient in bed during the digitalization.

The occurrence of syncope on changing suddenly from prostrate to the upright position may occur under the influence of digitalis, even with other lesions; the patient should be cautioned as to this.

Cardiosclerosis.—Digitalis is useless with a heart which has undergone marked fatty or fibrous degeneration. In this condition it is often contraindicated, because the overworked muscle is more readily poisoned.

High blood pressure has little bearing on the usefulness of digitalis. Its existence does not contraindicate the administration.

Acute Myocarditis and Endocarditis.—The use of digitalis is debatable: it can easily lead to dangerous overstrain of the hypersensitive muscle.

Coronary Insufficiency.—The effects of digitalization on the coronary circulation of animals are variable. The observations of Gold, Otto *et al.*, 1938, on 120 patients who had cardiac pain without congestive symptoms showed that changes in the pain or in the course of the condition occurred with equal frequency with a placebo as with digitalis. However, coronary infarcts in cats distinctly increased their susceptibility to the toxic actions of digitalis (Travell, Gold and Modell, 1937). In patients who have auricular fibrillation with *myocardial infarcts*, digitalis generally is more harmful than useful, tending to mobilize thrombi and produce embolism in the greater circulation (Askey and Neurath, 1945).

Aneurysm.—The sudden distention of the aneurysmal sac by a larger mass of blood, which would be the result of digitalis, is exactly contraindicated.

High altitude fatality is decreased by digitalization (E. Fischer, 1941; mice).

Digitalis in Infectious Fevers.—Fever does not modify the digitalis actions, the heart responding essentially as in nonfebrile individuals (Hirschfelder, 1920). Therapeutic doses have little effect on the febrile tachycardia, since this is due chiefly to increased metabolism. However, very large doses of digitaloids are required to produce cardiac stand-still (F. Herzog, 1930), owing perhaps to more rapid fixation of the glycosides in noncardiac tissues, such as in skeletal muscle and in liver, and their more rapid destruction. Digitalis would be indicated in fever patients with cardiac lesions, and particularly with auricular fibrillation. In the absence of these, however, its usefulness is doubtful (Hart, 1919).

The terminal collapse in fever is not due primarily to cardiac failure, but to capillary injury and blood concentration. When the heart muscle is affected, the injury is more profound than digitalis can correct; in fact, ordinary doses of digitalis are likely to become toxic to such hearts (for instance, with *diphtheria toxin* in guinea pigs and cats; Edmunds and Mayer, 1937) and digitalis is practically ineffective, just as in other forms of "shock" (G. Schwartz, 1906).

Digitalis has been prescribed in *pneumonia* as a prophylactic precaution against cardiac fibrillation (Cohn, 1915), but it is conceivable that it may dispose toward fibrillation, as it seems to do in diphtheria (Robinson). The parallel comparative study of Wyckoff, Du Bois and Woodruff, 1930, on nearly 750 pneumonia patients, showed a mortality rate of 34 per cent in the patients without digitalis, and 41 per cent in those with digitalis. Conservative doses of digitalis did not definitely influence the outcome, and the larger doses definitely increased the mortality, even when there was no direct sign of digitalis toxicity. Digitalis, therefore, does not appear advisable in pneumonia, except for the patients with definite auricular fibrillation.

Diuretic Action.—The digitalis drugs are potent diuretics in cardiac dropsies; the diuretic effect is proportional to the improvement of the circulation and to the absorption of the edemas. In all other conditions they have little or no effect on the urine. Practically negative results are obtained in normal individuals (Schwartz, 1906), in heart disease without effusion (Cohn, 1915) and in purely nephritic edemas (J. Miller, 1912). Moderate doses of digitalis have no effect on either the renal blood flow or the diuresis of normal animals; excessive doses slow the urine and blood flow, although they raise the blood pressure (Cushny and Lambic, 1921; externalized kidney, W. E. Reed).

The *factors involved in the improvement of the renal circulation* are mainly the relief of the venous pressure; the increased output of the heart; the increased "pulse pressure"; and the hydremia resulting from the absorption. These mechanical conditions cause corresponding increase of urine filtration even in dead kidneys (Sollmann, 1915).

Gremels, 1929, reported increased oxygen consumption by the kidneys and some diuretic action apart from circulatory changes in Starling heart-lung-kidney preparations; and Weese, 1934, concluded from the Rehberg method that digitalis diuresis involves diminished tubular reabsorption.

Gesell, 1913, found that artificial *changes in the pulse pressure* produced parallel changes in the excretion of urine, chlorides, urea and nitrogen.

Influence of Hydremia.—This is not the primary cause of the diuresis. Martinet, 1914, found that the viscosity of the blood and the protein content of the serum remain unchanged so long as the absorption of edema is in progress. When the edema has disappeared, but the diuresis still persists, the viscosity increases. Calvin *et al.*, 1940, reported that in patients with congestive heart failure the plasma volume falls during the diuresis induced by digitoxin.

TOXIC EFFECTS IN THE CLINICAL USE OF DIGITALIS

Digitalis is practically useless unless the dosage is sufficient materially to impair conduction; this impaired conduction is itself capable of causing arrhythmia, *i. e.*, of producing toxic effects. In other words, the full therapeutic effect practically coincides with the minor toxic manifestations (Eggleston, 1915). There is a fairly wide margin, however, between the therapeutic and the fatal dose (the therapeutic representing about one-third of the fatal; Robinson and Wilson, 1918); and the minor toxic effects do no permanent harm, if the dosage is reduced promptly on their occurrence. If they are disregarded, permanent irregularities may result. The emetic action furnishes a fairly efficient protection against overdosage by oral administration, but with intravenous injection fatalities are fairly common.

Digestive disturbances are important signals, since they occur early and are easily recognized. They consist in nausea, great malaise and often headache which may be very distressing. Vomiting occurs if the drug is continued. *Diarrhea* is not common with digitalis, is more frequent with strophanthus, squill and helleborein. When any of these digestive symptoms occur the dosage should be reduced or stopped. They subside in one or two days (Cohn, 1915).

With *normal individuals,* receiving standardized digitalis powder at the rate of 0.5 Gm., followed by 0.2 Gm. every six hours, intense nausea occurs when the total reaches 1.4 to 1.8 Gm. This also causes inversion of the T wave, and sometimes sino-auricular block (H. Feil, 1939).

Ratio of Emetic Potency.—With intravenous administration, Eggleston and Hatcher, 1913, found true digitalis the most emetic (emetic dose = 22 per cent of the fatal); then came strophanthus, ouabain, digitalis, digipuratum, digalen and adonis (ratio = 40 to 50 per cent); then digitoxin and amorphous strophanthin (58 to 65 per cent); least emetic were squill and apocynum (75 to 88 per cent).

Mechanism of the Emetic Action.—The nausea and emesis are not due to local gastric irritation, as was formerly thought. They set in only when the cardiac effects are manifest (Eggleston, 1913), and are perhaps best explained on the assumption that the emetic center is stimulated by reflexes set up chiefly by the cardiac actions (Hatcher and Weiss, 1923); in other words, the emesis seems to be a secondary manifestation of the cardiac action. It would therefore be useless to search for "nonemetic" digitalis preparations.

The *small importance of local irritation* is indicated by the fact that emesis occurs more readily with intravenous than with oral administration (Hatcher and Eggleston, 1912).

Very sensitive individuals may be nauseated by the acrid taste of even small doses, but local irritation sufficient to produce emesis could only occur with doses much larger than the clinical. The *digitonin* must play a very insignificant part, for it is not emetic in doses much larger than occur in the usual administration. The *fat* of the leaf is also nonemetic (Eggleston and Hatcher, 1913). The oil of strophanthus seed is emetic, but only in quantities 10,000 times as high as are present in a therapeutic dose of the tincture (Hatcher, 1916). *Squill* was formerly used as a nauseant expectorant; *euonymus* (wahoo) as cathartic.

The action is not directly on the vomiting center, for digitalis does not produce emesis if the spinal cord is divided at the second dorsal vertebra. If the brain is artificially perfused, emesis results from injection into the femoral vein, from where it cannot reach the brain; and emesis does not result if ouabain is added to the fluid that perfuses the brain, but does not reach the general circulation (Hatcher and Weiss, 1923).

The origin of the emetic impulses is disputed. Hatcher and Weiss, 1922, reported that digitalis does not produce vomiting if the heart is denervated, and the close correspondence of the emetic dose with that which produces cardiac disturbances suggests that these are the ordinary sources of emesis. However, Dresbach and Waddell. 1929, did obtain vomiting after cardiac denervation, and Hanzlik and Wood, 1929, found that emesis may arise from hepatic irritation. It has also been produced by applying digitalis to the peritoneum. It appears, therefore, that the emetic impulses may also be extracardiac. Indeed, Dresbach, 1941, throws doubt on the reflex explanation by a report that the emesis occurs not only after denervation of the heart, but of all viscera below the neck, and with about the same dosage as in normal animals. Nor is emesis prevented by denervation of the aorta, carotid sinus and carotid body (N. W. Pinschmidt 1946), or by pithing the spinal cord from the sixth thoracic vertebra downward (Haney and Lindgren, 1942).

Interesting antagonisms have been described. Hatcher and Weiss, 1927, found that *nicotine* prevents emesis from intravenous or intramuscular injection of digitalis, but not from intraperitoneal injection. As nicotine does not prevent emesis by apomorphine, they suggested that it paralyzes the afferent endings in the heart, but not in the peritoneum. The antagonism of nicotine to digitalis emesis persists more than three hours, while the other manifestations of nicotine toxicity disappear rapidly (N. B. Eddy and Hatcher, 1928). Neither atropine nor ergotamine prevents the digitalis emesis in pigeons (Hanzlik and Wood, 1929).

Visual Disturbances.—Purkinje in 1825 described flickering lines produced by full doses of digitalis (Hanzlik, 1925; F. D. Carroll, 1945). They are probably indirect results of the digestive or circulatory disturbances. Some patients complain of chromatopsia during clinical treatment. No fundus changes are observable, and the symptoms disappear on withdrawal (L. H. Maxwell and Mulberger, 1945).

Exanthemata.—A few cases of urticaria and scarlatiniform rashes have been reported after digipuratum and digalen

Cardiac irregularities from digitalis may simulate any of the clinical irregularities, so that it may be difficult to distinguish between them, particularly in advanced poisoning. To establish their causation by digitalis, it must be shown that they were absent before the drug was given, and that they disappear in a reasonable time after its discontinuance. The early effects, however, are fairly characteristic. The most common is excessive vagus stimulation (sinus irregularity). It is best seen when the heart is slowing after a little exercise. The rate may fall to 50 or even lower; so that syncope may occur between the contractions. The rhythm may remain regular; but ventricular extrasystoles are common. This stage would not occur in auricular fibrillation, or in absolute heart block. The next stage is usually *partial heart block* (Mackenzie, 1905), especially if the conductivity was naturally low. It may occur with relatively small doses (Windle, 1911), and may be permanent (Taussig, 1912); Christian, 1915, recorded transient auriculoventricular dissociation. The blocking by therapeutic doses of digitalis is apparently not additive to that of organic heart disease (Blumgardt and Altschule, 1939). The final stage is *muscular irritability*, first indicated by extrasystoles (Levine and Cunningham, 1920). These are particularly common in auricular fibrillation, giving the "coupled beats." With more advanced toxic action, there occur the same effects as in animals: high blood pressure (vasoconstriction); rapid rhythm, with periodic changes in amplitude, pulsus alternans (rarely).

Dosage.—Eggleston, 1912, found that the toxic effects depend mainly on the total dose, modified by the weight of the patient, absorption, individual susceptibility and the nature of the heart lesion. With the ordinary energetic administration, the characteristic coupled beats occur when the total quantity of digitalis has reached 2.25 to 6.25 Gm. Since the action persists partly from one to three weeks, these irregularities will recur with a smaller dosage.

Ratio of Toxic and Lethal Doses.—With intravenous injection, the lethal dose of any digitalis preparation is constant for cats. The toxic dose, however, varies with different animals. According to electrocardiograms, it ranges from 25 to 60 per cent of the lethal dose, averaging about 50 per cent. In any individual cat, however, it is fairly constant (Levine, 1919).

Duration of Irregularities.—This depends on the total dosage, and therefore on the severity of the phenomena. Eggleston, 1912, found that coupled beats generally outlasted the administration by four to twelve days; heart block, three to six; auricular fibrillation, three; muscular irritability, two; sinus irregularity, two days.

Fatalities with Intravenous Injections.—Deaths occurring within a few minutes to an hour after the injection of strophanthin or digitalis must be charged to these drugs, and are not uncommon (Rahn, 1920). They are probably due to ventricular fibrillation (Levine, 1919), which can apparently be induced in some diseased hearts, particularly those with impaired conduction, by the too abrupt introduction even of therapeutic doses (Robinson and Wilson, 1918; Levine, 1919), and especially by overdoses, *i. e.*, when insufficient allowance is made for previous digitalis medication. The course is too rapid to permit treatment.

The *intravenous injection of fatal doses of strophanthin into cats produces* vomiting, diarrhea, high rise of blood pressure, arrhythmia, then sudden ventricular fibrillation, with abrupt fall of blood pressure to zero, violent asphyxial convulsions, and death in a few seconds (Hatcher, 1909).

Fatalities from oral administration are rare with fractionated doses, since emesis sets in when one-third to two-thirds of the drug has been absorbed (Eggleston and Hatcher, 1913), and this would tend to prevent further absorption. Single massive doses (above 2.5 Gm. of the leaf) may be fatal.

The symptoms set in relatively late (one to twenty-four hours) and generally run a long course, so that a week or two may elapse before death. The symptoms are gastro-intestinal disturbances, slow and arrhythmic pulse, and the like, lassitude, muscular and sensory derangements. Death generally occurs suddenly, with dyspneic convulsions. Consciousness persists late. The *symptoms in mammals* are similar. The *treatment* consists in evacuation, quietness, possibly diffusible stimulants, and other symptomatic treatment. A cathartic should be given. The *fatal dose* varies greatly, on account of the variable absorption, the occurrence of vomiting, and so forth: 2.5 Gm. of digitalis have been fatal, while 4 Gm. have been followed by recovery (Lewin).

Delayed Deaths and Anatomical Injury.—If a large dose (about three-fourths of the acutely fatal) of a digitaloid drug is injected intravenously, many of the animals die several days later, with focal degenerative and necrotic changes chiefly in the papillary and trabecular muscles and the endocardial surface of the left ventricle. These are present to a less degree in the animals that survive. They were first observed in cats (H. Bauer, 1934; W. Lindner, 1939), but also occur constantly in dogs dying from cumulative poisoning by cardiac glycosides (Hu, Lieu and Li, 1936); in rabbits, only if they are first rendered anemic by bleeding (Remé, 1935). They are perhaps due to ischemia of the myocardium from prolonged coronary constriction; but similar and sometimes more severe degenerative and necrotic lesions are found in the brain, adrenals, kidney and liver (Hueper and Ichniowski, 1941). They have only been observed with toxic doses, and are not found in postmortem examinations of patients who have been under digitalis treatment (J. Travell *et al.*, 1942). Frogs poisoned with fatal doses show hyaline changes in the myocardium, but not focal necroses (Hu *et al.*, 1936).

DEVELOPMENT AND PERSISTENCE OF ACTION; FATE

Onset of Action.—When small therapeutic doses of digitalis drugs are administered by the alimentary canal, the effects develop slowly. It may be several hours before any action can be noted. The full effect is reached much later: twenty-four to thirty-six hours for the circulatory actions; seventy-two hours for the diuresis. This delay is due mainly to the insufficient dosage; *i. e.*, several doses must accumulate before the effective dosage is reached. When full therapeutic doses are given at once, as in the Eggleston method, definite effects (T wave) occur within two to four hours, and reach the maximum in six to twenty-four hours (Pardee, 1920). With therapeutic doses the *channel of administration* has relatively little effect on the onset of the therapeutic action (Pardee, 1925). The variations are probably within the experimental error, *i. e.*, absorption from the alimentary tract does not noticeably delay the development of the effects. This would not hold for strophanthus, which is generally absorbed more slowly; nor for the intravenous injection of strophanthin or ouabain, or of dangerous doses of digitalis: with these the circulatory response begins at once, and the diuresis starts in a few hours, although the maximal effects require somewhat longer (Hatcher and Bailey, 1910).

Absorption.—With oral administration, the rate of absorption increases with the *dose*, but is always quantitatively uncertain. The variation is especially great with *strophanthus* (Hatcher, 1909). This accounts for the unsatisfactory clinical results from the oral use of this drug. The safe dose would be so small as to be generally ineffective; a really effective dose could be highly dangerous, according to the individual absorption. *Helleborein* is probably not absorbed at all from the alimentary canal, since it commonly produces only diarrhea, without cardiac effects (Cushny, etc., 1912). Digitoxin appears to be better absorbed than digitalis (Eggleston, 1915) or strophanthin (Hatcher and Eggleston, 1919). The tincture of digitalis is absorbed more rapidly than the infusion. The chloroform-soluble extract is absorbed more completely and uniformly (Hatcher, 1920; Eggleston and Wykoff, 1922). Digipuratum and digalen are decidedly superior (Haskell, McCants and Gardner, 1916).

Different Portions of the Digestive Tract.—Quantitative studies by Ogawa, 1912, indicate that digitalis is not absorbed from the stomach. From the intestines, 34 to 45 per cent was absorbed in two hours from digitalis leaves; with digipuratum, the absorption was 52 to 61 per cent in two hours; 65 per cent in three hours.

Destruction in Alimentary Canal.—The digitaloids are practically unaffected by pepsin or trypsin (Goodall and Reid, 1914); but a small quantity of the glycosides, varying for the different glycosides, is destroyed by the acidity of the gastric juice; colloids tend to protect against this destruction (Hale, 1911; Brücke, 1936; Svec, 1937). Johannessohn, 1914, found that alkalis weakened only crystalline K-strophanthin; acids, this and amorphous K-strophanthin and strophanthus tincture. The amorphous strophanthin is changed mostly to strophanthidin, and partly to an inactive resin. Ouabain is unaltered by either acids or alkalis, which is an advantage in its administration. However, with the usual short contact, the destruction of the other principles is probably also unimportant (Hatcher, 1909). In the rat, with oral administration, strophanthin is mostly destroyed in the large intestine. Of digitoxin, also, variable amounts are destroyed before absorption (Hatcher and Eggleston, 1919).

Duration of Action.—The digitalis effects last for a long time after the administration has stopped, whether the drug was given by mouth or by vein. It is difficult to establish a time for the clinical action, because when compensation has been established it tends to persist, independently of the drug (except in auricular fibrillation), until some extra demand causes a fresh break of compensation. This probably holds true to some degree of the other cardiac changes. The effects of a "full" dose of digitalis or digitoxin seem to persist, with gradual decline, for one to three weeks, according to the total dosage; but for shorter periods with some of the other digitaloids, especially strophanthin and ouabain. Clinically, the duration of the actual digitalis action can be judged by the alteration in the T wave of the electrocardiogram. This persists from one to twenty-two days, averaging about nine days after discontinuance of the administration (G. C. Robinson, 1919). Other clinical facts lead to the same conclusion (Eggleston, 1912). Pardee, 1919, estimated the rate of disappearance in man, after full therapeutic doses, as averaging 0.15 Gm. of digitalis per day.

In *animals*, the duration of the digitalis effect can be measured accurately by Hatcher's method (differential fatal dose). In cats, one-half of the original effect of an intravenous injection persists for the following number of days: digitalis, five to twelve days; digitoxin, fourteen (dogs, two days; rabbits, less than one day); digitalein, three; digitalin German, three; digitalin true, less than two; ouabain and strophanthin, less than one (Hatcher, 1921). Klein, 1914, believed that the action of strophanthin may persist for a month in cats. The duration is much shorter in dogs and especially in rabbits, as quoted for digitoxin.

Apparently, the more resistant a species is to digitalis, the shorter is the action.

Cumulative Action.—The effects of digitalis tend to be cumulative, so that the same doses, continued day by day, tend to produce ever-increasing effects; or more commonly, toxic effects develop suddenly, without warning, after small doses have been continued for some time. In the therapeutic use, the dose must therefore be diminished, or toxic phenomena result, often abruptly. This cumulative action may be explained in part by the slow and uncertain absorption and excretion. The principal factor, however, is probably the slow, persistent and progressive action. Since the effects of a single dose may persist over several days or weeks, the effects of all the doses given in the meantime are more or less summed up; the effects of digitalis are determined by the total dose, and not by the single or even by the daily dose. The various cardiac glycosides differ in degree of cumulation. Those with the most persistent action are most cumulative, digitalis more than strophanthin (Li and Van Dyke); but the details are not well known.

Comparative Time of Action with Intravenous Clinical Injection of Digitalis Glycosides.—H. Gold *et al.*, 1943, reported that the *latent period* increases from ouabain (shortest), to digifolin, to lanatosid C, to digitoxin (longest); the *duration of action* is in the same sequence (ouabain shortest, digitoxin longest).

Chronic digitalis poisoning in animals was studied by von Lhota, 1910 to 1912, on dogs poisoned for several months by slowly increasing doses of digitalis. The phenomena correspond closely to those observed in man: the pulse after nine or ten days shows occasional short periods of slowing, but with the heart regular and strong. If the administration is continued, the slowing becomes more persistent and more marked and arrhythmic. Later, the pulse rate again increases to normal or somewhat above. The pulse changes outlast the administration for a long time; in severe acute poisoning, they may persist for several weeks; after chronic poisoning, they may last for over a month. The susceptibility to toxic doses increases (by the focal necrosis of the cardiac muscle), so that a smaller amount is fatal if it is given in fractions than if it is administered at one time (Lü, 1936). Typical cumulative poisoning has also been observed in cats (Klein, 1914). In pigeons, a single injection of digitalis, exceeding half the fatal dose, increases the glycogen content of the heart to about double. This is first noted about six hours after the administration and persists two days (F. Hahn, 1939).

Disappearance in the Body.—The digitaloids disappear from the blood almost immediately after the injection of even much more than fatal doses (Hatcher and Eggleston, 1912; Lhota, 1912). This rapid disappearance is due to wide distribution in probably all the tissues, for it occurs if the circulation is restricted to limited areas, but not if it is restricted to the heart and lungs alone. The liver plays perhaps a larger part than other organs. In rats, the greater part is fixed by the liver (Hatcher and Eggleston, 1919).

Excretion.—The digitaloids are partly destroyed in the body, mainly by the liver, and partly excreted unchanged. The excretion occurs chiefly through the bile, so that the substance may be demonstrated in the feces after intravenous injection. A small fraction is excreted by the kidneys. This increases if the bile duct is tied (Hatcher and Eggleston, 1919).

Combinations with serum proteins are formed by digitoxin and by the aglycones, but these do not influence the cardiac potency or lethal dose (A. Farah, 1945).

Fixation of Cardiac Glycosides in Heart Muscle.—The time and concentration relations of the cardiac actions involve peculiar characteristics connected with their penetration and fixation in the heart muscle, as revealed especially by quantitative studies on the "*Straub*" *excised frog heart* attached to a reservoir cannula (review, W. Straub, 1931, Lane Lecture). Even with this direct contact of the solution, there is a considerable delay before digitalis effects appear—about ten minutes or more, varying for the different glycosides—in contrast with most other drugs, such as muscarine, which act within a few seconds. The delay is not due to slow penetration, for increase of concentration does not shorten the incubation period below the minimum characteristic for each glycoside—although dilution may lengthen it (Straub, 1910 and 1913), as may also decrease of the total quantity of glycoside (Clark, 1912). If the heart is removed from the digitalis solution in one minute when no action is perceptible, the cardiac arrest will occur in the ten minutes, just as if the heart had been left in the digitalis solution. The full toxic amount has therefore been absorbed in one minute, but the effects appeared only after some ten minutes. Conversely, the muscarine effects can be removed almost immediately by washing, but the digitalis effect persists in spite of prolonged washing, indicating that the glycoside is firmly bound in the heart in such form that it continues its action. With small doses, the heart may indeed appear to recover completely on washing, but when immersed anew in digitalis solution, even after a long time, its threshold is found lowered (Gottlieb, 1914; Issekutz, 1915). The recovery of intact animals from subfatal doses is probably due to gradual destruction of the poison in the muscle metabolism, rather than to "washing out."

The retention capacity varies for the different glycosides, inverse to their solubility in water. It is much less for the aglycones. The amount bound is small in any case (Holste, 1912); somewhat greater with digitalin than with strophanthin (Weizsaecker, 1913). Fuehner, 1912, found thamethyl violet, which has a typical digitalis effect, act cumulates in the cardiac muscle of frogs, the effects corresponding to the quantity of dye so fixed.

Isolated hearts of embryonic chicks, when arrested by digitalis, recover completely on washing with Tyrode solution. Digitoxin is more, ouabain less, persistent than digitalis (Paff and Johnson, 1940).

Perfused mammalian hearts (Starling cat preparation) show similar fixation. The actual amount of glycosides they take up from the blood is limited to that which is fatal to the heart (Genuit, 1935). Anything beyond this remains in the blood. Smaller amounts are taken up completely, if sufficient time is allowed, the speed depending on the concentration.

In the intact body, other tissues compete with the heart for the glycosides. Their affinity is less, per gram of tissue (about 1/4 for skeletal muscle, 1/5 for liver, 1/2 for kidneys); but because of their greater mass, they can dispose of considerably more than the heart. With intravenous injection of just fatal doses, only 1/20 to 1/10 of the different digitaloids is bound in the heart (H. Weese, 1928 to 1933; Genuit, 1938), and the remainder by the tissues, especially the skeletal muscle, but also in the liver and other viscera (Hanzlik and Wood, 1929). For this reason, intra-arterial injection, which passes through muscle before reaching the heart, requires much larger doses than intravenous injection. For the same reason, the fixation in the heart is completed in the first passage of blood through it—what is not bound then is lost to the other organs.

The ratio bound by extracardial tissues varies for different glycosides, and the ratio of the concentration which arrests excised papillary muscle, to the lethal dose on intravenous injection for cats, being twenty times higher for digilanid C than for ouabain and for digitoxin (Cattell and Gold, 1939).

The *persistence of active glycoside within the heart muscle of mammals* is shown by the greater susceptibility of Starling heart preparations from animals which had previously been treated with these drugs. With digitoxin, this could be demonstrated for some weeks; with ouabain for fifty-four hours; with scillaren A for two hours. Earlier evidence for such persistence had been brought out by Cloetta and Fischer, 1906, and Hatcher, 1912.

ADMINISTRATION OF DIGITALIS DRUGS

Digitalis is usually started after decompensation has occurred. It is then desirable to induce the effects as promptly as may be safe, and to maintain them as long as necessary. Intravenous administration would be the promptest method, but it has drawbacks that restrict it mainly to emergencies. Ordinarily, the objects are fully met by proper oral administration. In this, it is necessary to remember the long duration of the digitalis action, and the consequent cumulative action. It must be emphasized that the total accumulated dosage is of more importance than the single doses; that practically no therapeutic effect is produced until the total dosage approaches the toxic; that the dosage must be reduced when the desired action has developed; that the patient must therefore be closely watched. He should be seen at least daily, while under active medication; the intensive methods are safest under hospital conditions. If toxic symptoms appear, the administration should be temporarily suspended; *i. e.*, if nausea develops; if the pulse falls below 50; or if any of the characteristic digitalis irregularities arise. In the intensive methods it is indispensable to employ digitalis preparations of known activity, tested first on animals, and then checked by cautious observation in the clinic. The dosage should be measured accurately, and not estimated by "drops." Febrile temperature renders the heart more susceptible to digitalis, so that the dosage should be reduced.

The **quantity of digitalis present in the body** determines the response. It may be calculated by subtracting the total quantity destroyed (estimated at 1.5 cc. of the tincture per day, multiplied by the number of days since the administration started) from the *total* quantity of tincture administered within the preceding two or three weeks. The result is only a rough approximation, since the rate of destruction is not constant, but varies, for instance, with the quantity present (Gold and DeGraff, 1929); but it furnishes the best available estimate of cumulation. The student will profit by working out the following problems:

Problems of Digitalis Retention.—1. A patient has received by the cumulative method, 4 cc. of tincture per day for the first week; 3 cc. of tincture per day for the second week, none for the third week.

Assuming that digitalis disappears from the body at the average rate of 1.5 cc. of tincture per day; and assuming the "toxic dose" at 22 cc. of tincture (actually present in the body), what percentage of this amount is present at the end of the first, second and third week?

2. If he received 6 cc. per day, and destroyed it at the above rate, how soon would he reach the toxic dose?

3. How long must it then be withheld before the quantity retained falls to one-third of the toxic dose?

Systems of oral administration may be grouped as intensive, cumulative, constant dose and maintenance methods. The intensive methods aim to give the greater part of the total dosage at once, and practically the whole within a day. The cumulative methods accumulate the effective dosage by divided doses in two or three days. The constant dose methods tend to err on the side of safety, and often do not reach the effective dosage at all. The intensive methods are most effective, and under the best hospital conditions are probably the most satisfactory. The cumulative method occupies a middle ground.

Intensive Method.—Eggleston, 1915, determined the total dosage of standardized digitalis necessary to produce full therapeutic or minor toxic effects, as 0.15 "cat units" per pound of body weight. This corresponds approximately to 1.5 Gm. of the official Powdered Digitalis or 15 cc. of the Tincture per 100 pounds of body weight (⅓ cc. per Kg.). Eggleston therefore proposed to give half of this dose at once (*i. e.*, 7.5 cc. of standardized tincture per 100 pounds, or 1¼ minims per pound); followed in six hours by one-fourth of the total dose, then smaller fractions (*f. i.*, dividing the dose each time successively by ½), every fourth to sixth hour till the total dosage or full response is reached. This has been somewhat simplified in practice, practically disregarding body weight with adults; for instance, 0.5 Gm. of powdered digitalis for the first dose, followed by 0.2 Gm. every six hours till a definite effect is observed, as nausea, apex rate, diuresis or diarrhea. This requires a total of 1.4 to 2 or even 3 Gm. in the course of two or three days. The response starts definitely in two to five hours after the first dose, reaching its maximum within twenty-four hours, and continuing without further administration for four to fifteen days.

The *relation of therapeutic effects to dosage* was worked out by Eggleston, 1915, in terms of "cat units"; a "*cat unit*" corresponding to the quantity of the drug per kilogram of cat, that is just fatal by intravenous injection under suitable conditions (Hatcher, 1910). Eggleston found that the relation of effect to dose (cat units) is remarkably uniform for a given drug, regardless of the presence or nature of cardiac disease. Whatever the condition, the total dose of digitalis by mouth, to the appearance of the first improvement, averages 0.09 cat units per pound of body weight (about 0.9 Gm. of good digitalis per 100 pounds); for full therapeutic or minor toxic effects, 0.146 cat units per pound (about 1.5 Gm. per 100 pounds). With digitoxin, the corresponding doses are: first improvement, 0.04 cat units per pound (1.4 mg. per 100 pounds); full therapeutic effect, 0.066 cat units per pound (2.3 mg. per 100 pounds). The other digitaloids give variable results, by mouth, because of uncertain absorption. They are therefore unsuited for the intensive oral method. By vein, however, a cat unit of all digitaloid substances is equally potent.

Cumulative methods start with a *daily dose* equivalent to 3 to 6 cc. of the Tincture of Digitalis (MacKenzie and Cushny), divided into three or four portions, and continued until the desired effect is obtained, when the dose is reduced to the maintenance dosage.

Maintenance Dosage.—When decompensation is only temporary the improvement is often lasting, and the digitalis may be discontinued when compensation has been restored. In auricular fibrillation, however, it is necessary to keep up a continuous digitalis effect. Ambulatory patients respond to about half the dosage needed for seriously ill patients (Gold and DeGraff, 1930). Clinical experience has shown that this should not exceed the daily dosage of 1 cc. of Digitalis Tincture (A. Fraenkel, 1907). This is not quite equivalent to the capacity of destroying digitalis, which Pardee, 1919, calculated to average 1.5 cc. of Tincture (1 cc. = 1 cat unit). There is therefore little danger of cumulation.

Continuous Methods.—The older methods of using digitalis employed a dosage approximating the maintenance dosage. This would be unsuccessful, except when employing preparations stronger than the standard.

Rectal administration may be used when oral administration is not feasible; for instance, because of emesis. The absorption is at least as rapid as with the oral route, and the dosage is the same. The alcoholic tincture is too irritant to be retained, so that an aqueous extract must be employed (R. L. Levy, 1924; Zondek, 1925).

Hypodermic or intramuscular administration should be avoided, because of local irritation; nor is the absorption materially more rapid than with the intensive oral method (Barley, 1909).

Intravenous Administration.—Prompt results ensue if a *full* dose (corresponding in effect to the "intensive" oral dosage) of strophanthin, ouabain or appropriate digitalis preparation is injected by vein. A few patients are very resistant, although absorption does not come into play; but ordinarily in auricular fibrillation definite slowing may be perceptible in five minutes and becomes marked in fifteen minutes, nearly maximal in half an hour, and maximal in two to three hours, and remains at this level for twelve to twenty-four hours. The T wave is reversed in two to four hours. Diuresis begins in a few hours (Wyckoff and Goldring, 1927, ouabain; Pardee, 1928, digitalis preparations). This avoids the delay incident to oral administration, but is distinctly more dangerous, especially if the heart has not been thoroughly studied (G. C. Robinson, 1912), and if information as to previous medication is incomplete. Intravenous administration should not be used routinely, but only if the patient is critically ill, so that it is imperative that full digitalis effect be secured in less than the two hours which would be required by the intensive oral method; or if the patient is unable to retain digitalis by mouth or rectum. The *full intravenous dosage* on the basis of 150 pounds

(70 Kg.) body weight is $\frac{1}{2}$ mg. of ouabain, or 1 mg. of strophanthin, or 15 cc. of digitalis preparations standardized to correspond to the tincture (or 1.2 mg. of digitoxin); but the full dosage should be fractioned, *giving half at the first injection* and the remainder in fractions of $\frac{1}{10}$ to $\frac{1}{8}$ of the full dose, at intervals of two hours, if necessary. When a satisfactory response has been secured, these injections ($\frac{1}{10}$ to $\frac{1}{8}$ of the full dose) may be continued at four to six hour intervals; but it seems safer to follow the first dose (*i. e.*, half of the full dose) with oral administration of 0.3 Gm. of digitalis, or 3 cc. of the digitalis tincture, or 0.1 to 0.2 mg. of digitoxin, every four hours till the therapeutic result is obtained.

Recapitulation of Time of Clinical Onset and Duration

Method of Digitalis Administration	The Effect			
	Becomes Perceptible (After Starting of Administration)	Becomes Complete (After Starting of Administration)	Persists after Discontinuance	
			Practically Complete	Partial
Oral, cumulative......	12 to 24 hrs.	24 to 72 hrs.	4 to 15 days	1 to 3 weeks
Oral, intensive........	2 to 4 hrs.	12 to 24 hrs.	4 to 15 days	1 to 3 weeks
Vein, intensive.......	5 to 15 min.	2 to 3 hrs.	12 to 24 hrs.	....

The full or half dosage should not be injected unless it is definitely known that the patient has not received digitalis during the last two weeks. *If digitalis has been taken, the dosage should be reduced* according to the amount calculated as remaining in the body. If no data are available, the one-tenth full dosage (*i. e.*, 0.1 mg. of strophanthin or 1.5 cc. of the digitalis preparations per 150 lb. body weight) may be injected and repeated at intervals of one-half to three-quarter hour until the therapeutic response is secured; this is safe, but may not gain any time over oral administration. Doses smaller than these (0.1 mg. of strophanthin or 1.5 cc. of the digitalis preparations) produce little effect on the heart rate in auricular fibrillation, and no effect on the T wave, unless the patient is already partly digitalized.

Intravenous digitalis therapy was tried clinically by Kottman and by Mendel in 1905, but the preparations they employed were not satisfactory. The method was put on a better basis by the introduction of strophanthin (A. Fraenkel and Schwartz, 1907). Intravenous injection sometimes produces cyanosis, chills and slight fever.

DRUGS AND PREPARATIONS OF THE DIGITALIS GROUP

Choice of Preparations.—Everything that can be accomplished in heart disease by drugs of this group can be secured with the official powder and tincture of digitalis for oral, and strophanthin or ouabain for intravenous, administration, quite as well as by any of the other drugs. The therapy of heart disease is probably better served at this time if the practitioner confines his prescribing to these official preparations, thus gaining a thorough experience with them, than if he dilutes and probably confuses his experience with the large variety of other drugs, preparations and isolated principles. These may sometimes succeed when the others have failed, but this is generally because the dosage was inadequate until the added dosage of the new drug brought it to the therapeutic threshold. It is possible that some of these may have special advantages, but so far at least these are not sufficiently clear to balance the confusion of their multiplication.

Preparations of Digitalis.—The powdered standardized leaf (*Digitalis Pulverata*, U.S.P.), dispensed in tablets, is perhaps the best form of oral digitalis medication. It avoids the taste of the tincture, and is stable if kept reasonably dry. *Digitalis Tincture*, U.S.P., which is also standardized, has some advantage when the dose is being adjusted. It does not deteriorate materially within a year. Variations in the alcoholic strength of the menstruum between 35 and 95 per cent make little difference. The *Fluidextract* is unreliable

The *Infusion* has been dropped from the U.S.P. It is active, but dangerously variable, and as dispensed it is often unreliable. It does not keep. All the glycosides are extracted from the leaves by either hot or cold water; but according to Straub, hot water destroys part of the amorphous active glycosides (the gitalin fraction) so rapidly that the infusion made by heat is materially less active than that made with cold water. Hatcher, however, found the same activity in both.

Deterioration of Digitalis.—The principles are stable when dry or in alcoholic solutions; but like all glycosides, they are subject to decomposition in the presence of water, especially by bacteria, moulds or acids. This results in loss of activity; but Hatcher and Eggleston, 1915, found the infusion practically unchanged a week or longer under ordinary conditions. The addition of alcohol is not necessary. *Acids are incompatible* with the *digitaloid glycosides.*

Tinctures and other preparations containing at least 50 per cent of alcohol generally keep satisfactorily, their deterioration averaging perhaps 10 per cent per year (Hamilton, 1918). There are marked discrepancies, however. Haskell *et al.*, 1923, found that a tincture kept five years under store conditions had not lost any activity. The storage temperature is a material factor (Newcomb and Rogers, 1918).

The *dry leaves*, so long as they are not mouldy, keep indefinitely (Sharp and Lankaster; Hatcher and Eggleston, 1913), without the necessity of the elaborate precautions advocated by Fock, 1906. They are not injured by heat of 120° C., but suffer above 140° (Hale, 1911).

GALENICAL PREPARATIONS OF DIGITALIS.—*__Digitalis Pulverata__, U.S.P. (Foxglove), represents the leaves of Digitalis purpurea dried, powdered, and adjusted by bio-assay with an intravenous cat method so that 0.1 Gm. equals 1.0 U.S.P. digitalis unit. Dose, 0.1 Gm., 1½ grains. *Digitalis Capsules*, U.S.P., and *Digitalis Tablets*, U.S.P., are usually available as 50 and 100 mg. (¾ and 1½ grains). The United States Pharmacopoeia Digitalis Unit is identical in potency with the International Digitalis Unit, adopted in 1928 by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations. One International Digitalis Unit represents the activity of 0.1 Gm. of the "International Standard Digitalis Powder." The reference standard and the assay method differed for successive revisions of the U.S.P., that of the XI being something like a fourth more potent than the preceeding and succeeding editions (G. G. Nelson, 1941; H. Gold and Cattell, 1943). The activity of different samples of digitalis varies considerably, so that they should be standardized by bio-assay. The leaves of the first year plants are as good as the second (Sharp and Lankaster; Caesar and Loretz, 1910). Plants cultivated in America (Newcomb, 1912) are as good as the wild European (Rowntree and Macht, 1916). Those grown during a wet season are less active (Caesar and Loretz, 1907). The petioles, ribs and hairs of the leaves are relatively inactive (Newcomb and Rogers, 1918). Other species of digitalis, *e. g.*, *D. Thapsi*, also have the actions of the group (Farwell and Hamilton, 1917). White and Morris, 1918, claimed that *D. lutea* is as effective as purpurea on the heart, and appears to be less emetic and less convulsive. *__Tincture of Digitalis__, U.S.P., represents 10 per cent of drug, and is standardized to contain 1 digitalis unit per cc. Dose, 1 cc., 15 minims. Tinctures deprived of fat do not become turbid when mixed with water, but have no other advantage.

Injectable digitalis preparations are solutions of the partly purified water-soluble principles, generally the gitalin fraction. They have no advantage over ordinary digitalis preparation for oral use. It may be questioned whether they are superior to strophanthin for parenteral use, although their action is more lasting.

The U.S.P. has a title of "*Digitalis Injection*," without further identification except that it is "a sterile solution of a mixture of glycosides or therapeutically desirable and cardio-active constituents of digitalis in water for injection." Its potency is to be indicated in U.S.P. units. A working formula was published by Hatcher and Haag, 1929. A number of *proprietary preparations* are listed in N.N.R. (Digitan, Digalen, Digifolin). Comparisons of the potency of digitalis specialties by the pigeon method were published by A. J. Lehman and Hanzlik, 1933.

Digalen ("Digitoxin soluble," Cloetta, 1904) was widely advertised as an amorphous and soluble isomer of digitoxin. Kiliani, 1907, stated that it consists mainly of digitalein Schm.; his opinion should carry weight. It was said to be free from the disadvantages of digitoxin; but it is of variable activity, unstable (Hale, 1910), produces considerable irritation, is not suitable for hypodermic injection and causes cumulative effects (Fraenkel, 1907; Westenrijk, 1908). It therefore has no real advantage over a good tincture (Dixon, Cow, 1912), except for venous injections, which cause pain and sometimes thrombosis. It is marketed as ampuls for injection (1 cat unit in 2 cc.), and as a solution for oral use (1 cat unit in 1 cc.), and as tablets of ½ and 1 cat unit.

Digitan (Digipuratum) is a purified solid extract containing chiefly the tannates of digitoxin and digitalin, freed from digitonin, and standardized to the same activity as digitalis leaves. It is relatively nonirritant (Dixon, 1912; Cow, 1912). It is marketed in ampuls for intramuscular (not intravenous) injection, 0.1 Gm. in 1 cc.; and as tablets, 0.1 Gm., for oral use.

Isolated digitalis glycosides proved rather disappointing. None appears to be more efficient, or quicker in action, or more prolonged or less toxic than the standardized leaf (Stroud and Van der Veer, 1937). They are difficult to obtain pure, and many commercial medicinal preparations are of uncertain activity. Digitoxin, however, has aroused renewed attention, especially in the form of "Digitalin Nativelle."

Digitoxin is probably the most important constituent of the leaves, in activity and in quantity (0.22 to 0.4 per cent). It is crystalline, but Cloetta found that the best commercial products are impure; and the medicinal may contain only one-third of digitoxin. It has the undesirable features of producing excessive irritation, and of being nearly insoluble in water. It may be dissolved in 25 per cent of alcohol.

Digitoxin, U.S.P., is "either pure digitoxin or a mixture of cardio-active glycosides from Digitalis, consisting chiefly of digitoxin," assayed against the U.S.P. Digitoxin Reference Standard. It is a microcrystalline powder, insoluble in water, soluble in alcohol (1:60). Average dose, oral, 0.1 mg. (1/600 grain). *Digitoxin Injection,* U.S.P., a solution in 40 to 50 per cent alcohol, for intravenous injection. Usual size, 0.1 mg. in 1 cc. *Digitoxin Tablets,* U.S.P.; usual sizes, 0.1 and 0.2 mg. "*Digitaline Nativelle*" appears to be a reliable form of crystalline digitoxin. It is absorbed practically completely from oral administration, so that the full therapeutic effect in patients with auricular fibrillation is the same for oral and intravenous administration, 1.26 mg. equal to 3 cat units; while 15 units or 1 Gm. of powdered digitalis are necessary for the same effect. The full amount of this digitoxin may be administered in one dose, which would not be safe for digitalis. Intravenous administration acts somewhat more promptly than oral, but in three or four hours the effects are about the same. The incidence of toxic manifestations appears somewhat lower for the oral digitoxin than for the leaf. The cardiac slowing is apparently less and shorter than with the leaf. The cumulative action is similar. The most favorable maintenance dose is 0.2 mg. per day (H. Gold *et al.*, 1942, 1944; L. N. Katz and Wise, 1945). It is marketed in *Tablets* of 0.1 and 0.2 mg., and in *Solution,* 1:1000 (1 mg. per cubic centimeter).

Gitalin (Verodigin), the *amorphous* constituent of the leaf, prepared according to the method of Kraft, is marketed as tablets of 0.8 mg. (1/80 grain), equal to one cat unit.

Digoxin, U.S.P., is a glycoside obtained from the leaves of Digitalis lanata or orientalis by hydrolytic removal of the acetyl and glucose groups from Digilanid C, and assayed against the U.S.P. Digoxin Reference Standard. It is insoluble in water. It is used especially for rapid digitalization. The average oral dose is 0.5 mg. *Digoxin Tablets,* U.S.P., are usually available as 0.25 mg. *Digoxin Injection,* a solution in 70 per cent alcohol, for intravenous administration, is usually available as 0.5 mg. in 1 cc.

Lanatoside C, U.S.P. (Cedilanid), is a glycoside from the leaves of Digitalis lanata. It is slightly soluble in water (1:20,000). Average oral dose, 0.5 mg. *Lanatoside C Tablets,* U.S.P.; usual size, 0.5 mg. *Lanatoside C Injection,* U.S.P., in 70 per cent alcohol, for intravenous administration. Usual sizes, 0.4 mg. in 2 cc., 0.8 mg. in 4 cc. *Lanatoside C Tablets,* U.S.P.; usual size, 0.5 mg.

Digilanid, a mixture of the "original" crystalline glycosides of Digitalis lanata, isolated by Stoll, is claimed to form a stable solution which can be injected by vein or hypodermically, and to be readily absorbed from the alimentary canal. It is marketed as *Solution,* in ampuls of 2 and 4 cc., each cubic centimeter equal to 0.2 mg. or 0.6 cat unit; and as *Tablets,* 0.33 mg. = 1 cat unit. The daily cumulative dose is 2 to 4 tablets, or 2 to 4 cc. of solution, until therapeutic or minor toxic effects appear. Then the dosage may be reduced to half.

Digitalins.—The uncertain composition of these mixtures, and the danger of confusing the similarly named but very different preparations, should preclude their use. At least, "digitalin" should never be prescribed without specifying the variety (verum, German, French, and the like).

Digitalin "True" is almost insoluble and not irritant. Clinically, it has proved too feeble, a variable quantity being probably decomposed in the stomach (Deucher, 1896). It has been used in *doses* of 1 to 3 mg. per day; even 50 mg. have been given without toxic effects (Pfaff, 1892). It is administered in pills or dissolved in dilute alcohol.

Strophanthins have the advantage of being less irritant and less cumulative than digitalis; but the absorption is so uncertain that their use by mouth is not advisable (Hatcher and Bailey, 1909). This is reflected in the different doses of strophanthins used by various clinicians. It is also liable to produce diarrhea. The main field of the strophanthins is for intravenous injection. Ouabain has the advantages that its identity is assured.

Ouabain, U.S.P., g-Strophanthin-Crystalline, was originally obtained by Arnaud from Acokanthera Ouabaio, which was used as arrow poison in East Africa (Santesson, 1928); now generally from Strophanthus gratus. Assayed on cats to equal the U.S.P. Ouabain Reference Standard. Soluble in water (1:75) and in alcohol; difficultly in fat solvents. Dose, for intravenous or intramuscular injection, 0.25 to 0.50 mg., not to be repeated in less than twenty-four hours. *Ouabain Injection,* U.S.P., in water for injection; usual sizes, 0.25 and 0.5 mg. in 1 cc.

***Strophanthin,** U.S.P. (Strophanthinum; Amorphous or k-Strophanthin); a glycoside or mixture of glycosides from Kombé Strophanthus. Very soluble in water or diluted alcohol; nearly insoluble in fat solvents. Standardized by bio-assay on cats to a potency of 50 per cent of the U.S.P. Ouabain Reference Standard. It is about a third more potent than in U.S.P. XI (Vos and Braun, 1945). Dose (daily), intravenous or intramuscular, 0.5 mg. *Strophanthin Injection,* U.S.P., in ampuls, of 0.5 mg. in 1 cc.

Apocynum and Cymarin.—The rhizome and roots of Apocynum cannabium, *Canadian Hemp,* produce potent digitalis effects and have been used as a fluidextract (average dose, 0.75 cc., 12 minims).

Cymarin, the active constituent, has been used clinically like strophanthin, by vein or muscle, 0.1 to 0.5 mg.; hypodermic injection is too irritant. It is difficultly soluble in water, easily in alcohol. It has also been given by mouth, 0.3 mg., three to five times daily (von Noorden, 1916; bibliography). Gaisböck, 1915, on the basis of his clinical and experimental studies, emphasized the need of caution in its use. The drug could probably be spared. Its *actions* agree with those of digitalis (Dale and Laidlaw, 1909, who studied the pure principles). The cardiac action, therapeutic and toxic, of cymarin (frog, Kuroda, 1914; electrocardiograph, Hecht, 1915) is somewhat weaker than that of strophanthin. It produces practically no irritation, but relatively strong vasoconstrictor effect. Kuroda claims that the cumulative and emetic effects are weak; but Taviani, 1915, found the serious disadvantages of uncertain absorption, and variable strength of the commercial cymarins. Large doses are also nephritic. Beco and Dossin, 1919, with intravenous injections in dogs confirmed the slowing, by vagus stimulation (central and peripheral); but claimed that the cardiac tonus was decreased, and never raised. The blood pressure rose by general vasoconstriction, especially splanchnic (direct action on vessels). The urine flow was hindered, the renal vessels being constricted even by minute doses.

Scilla (*Squills*) produces the same effects as digitalis, experimentally and clinically (in auricular fibrillation). The dosage required to produce the typical response of heart block and reversal of T wave is from 24 to 48 cc. of tincture per day (Viko, 1920), *i. e.*, considerably larger than the official dose. Toxic symptoms are rare. The milder action and larger dosage are due to poor absorption, for the intravenous dose is about the same as for digitalis (Eggleston). The poor absorption renders it undesirable as a digitalis substitute (Dixon, 1906), although it was advocated by Haynes, 1906. Scilla was formerly used as expectorant (nauseant) and general diuretic. It is not well suited to either purpose. There are much safer expectorants; and diuresis occurs only when cardiac edema is relieved (Viko).

Squills contains a crystallizable cardiac glycoside *Scillaren A*, which is sparingly soluble in water, and an amorphous fraction, *Scillaren B*, which is marketed for therapeutic use. A mixture of all the glycosides is marketed as "*Scillaren*." The action is less persistent and therefore less cumulative than that of digitalis, and it is claimed to be more diuretic, perhaps by a direct action on the renal epithelium. The official Scilla is collected from the countries on the north shore of the Mediterranean and is known as "*White Squills*." Another variety of the same plant which grows in Algeria yields "*Red Squills*," which is widely used as a rat poison. It contains the same cardiac glycosides in about the same quantity, but it also contains scilliroside, a glycoside with digitalis actions, apparently absent from the White Squills, that is toxic to rats, causing deaths after some days of alternating convulsions and paralysis (F. R. Winton, 1927; F. S. Philips, 1946). A product about a hundred times more toxic to rats has been obtained by extraction with 80 per cent alcohol (Leblanc and Lee, 1939). "*Urginea*," B.P., a distinct species, has the same effects as the White Squills, and is used in India in the same dosage.

Squill, N.F. (Scilla), is the dried fleshy scales of the bulb of the white variety of Urginea maritima (Urginea Scilla, B.P.). Dose, 0.06 to 0.2 Gm., 1 to 3 grains. The *Compound Syrup*, N.F., contains in each 2 cc. (30 minim) dose 0.16 cc. of fldexts. of squill and senega and 4 mg. of tartar emetic.

Scillaren, N.N.R., is a mixture of the natural glycosides of fresh squill. Sparingly soluble in water, the action is apparently less lasting than with digitalis. Oral dose, 1.6 mg. three or four times daily till effective; then half this dosage. Marketed in tablets of 0.8 mg., and solution of 0.8 mg. in 1 cc. *Scillaren B*, N.N.R., an amorphous natural glycoside from fresh squill, and as *solution* for intravenous injection, in ampuls of 0.5 mg. in 1 cc. *Dose*, not to exceed 0.5 mg. in 24 hours. *Urginin*, N.N.R., a mixture of two water-insoluble glycosides from squill. Oral maintenance dose, 0.5 to 2 mg. daily, as *Tablets* of 1 mg.

Thevetia Glycosides.—The fruit of a South American tree, Thevetia neriifolia, "Yellow Oleander," contains cardiac glycosides, principally *Thevetin*, isolated by De Vry, 1863, and studied by König and Hasemann, 1876, and recently by Chopra and Muckeyee, 1933, and by Chen and Chen, 1933 and 1934. It is soluble in alcohol and in water, and the watery solution is fairly stable. It produces typical digitalis actions, but it does not appear to have any special advantage. Its potency is about an eighth that of ouabain, measured on cats. It is too irritant for oral administration, but may be administered intravenously, 2.75 mg. three times daily, till the therapeutic effect is secured. A second glycoside, *thevetoxin*, has been isolated. Its actions are similar, but less potent (Bhatia and Lal, 1934).

Toad Poisons.—The dermal glands of toads secrete several kinds of toxic substances, differing in importance in different species (review, O. Gessner, 1938): (1) *Digitaloids*, cyclopenteno-phenanthrene derivatives, the *bufotoxins*, the aglycones *bufagins*, and the *bufotalins*, probably formed from cholesterol, closely related to the digitalis glycosides in structure as well as in action (especially scillaridin; Chen and Chen, 1933). Frog skin also has a weak digitalis action (Fuehner, 1910). (2) *Several alkaloids*, not present in sufficient quantities to exert any action: bufotenine (Handovsky, 1920); bufotenidine, bufothionine; a few species contain epinephrine. (3) A variety of other compounds with local irritant action.

Resistance of Toads to Cardiac Glycosides.—Toads tolerate much higher doses of all cardiac glycosides than do frogs (150 times as much ouabain). The tolerance is localized in the cardiac tissue. They are somewhat more resistant than frogs to picrotoxin, strychnine, cocaine and pentobarbital, but have about equal susceptibility toward other drugs acting on the central and autonomic nervous systems, and toward curare (Chen and Chen, 1933).

Bio-Assay of Digitalis and Related Drugs.—Different samples of the crude drugs differ seriously in potency, and they must be adjusted by bio-assay to uniform potency by comparison with an international reference standard sample of the drug. The "International Unit," which is official in the U.S.P. and B.P., corresponds to 0.1 Gm. of this standard digitalis powder. Various methods of bio-assay are available, giving often discordant results because they differ in principle, especially as to absorption, sometimes as to criterion of action. They are, moreover, complicated by technical difficulties, so that the prescribed minutiae must be meticulously followed.

The current U.S.P. directs a fatal dose "*intravenous cat method*," which measures the concentration of active principles since the end point, the sudden cardiac arrest, is a specific digitalis effect; but it entirely disregards absorbability, and therefore is misleading for the oral dosage of different digitalis principles. It is fairly reliable for different samples of the leaf and tincture, since the ratio of glycosides does not usually vary widely.

The U.S.P. digitalis bio-assay, in principle, macerates the powdered drug (and the standard) with an alcoholic medium. The solution is infused by femoral vein into lightly etherized cats, in fractional doses five minutes apart, until cardiac arrest occurs after 13 to 19 doses. At least a dozen cats are required for a complete test. The *U.S.P digitalis unit* is the amount which equals 0.1 Gm. of the U.S.P. standard reference powder. It is identical with the International Unit, but is a third stronger than the "cat unit" of Hatcher, 1916, which is the amount fatal to 1 Kg. of cat, as determined by the original method.

The intravenous cat assay was introduced by Hatcher and Brody, 1910, and has been variously modified, especially as to anesthetic and rate of injection (Magnus; Van Wijngaarden, 1926; Burn, 1928). The influence of *anesthesia* is reported by Holck *et al.*, 1945. The fatal dose is almost 50 per cent higher with dial or pentobarbital than with ether anesthesia; with urethane it is 20 per cent higher than with ether. The *age* of cats does not affect their susceptibility (Haag and Corbell, 1940). Statistical analysis shows that ten and eleven cats each for the standard and specimen are required to obtain an approximation of plus or minus 20 per cent. Most experienced assayists can distinguish a difference of 20 per cent, but not of 15 per cent. The $LD_{(50)}$ of the U. S. standard reference powder is 0.77 units per Kg. of cat (C. I. Bliss, 1944).

Although the cat assay disregards absorption, its potency accords fairly well with the oral clinical assay (average divergence of 44 per cent), but not for isolated principles (Cattell and Gold, 1944).

Intravenous assay may also be made on *other mammals* (dogs, McGuigan and McGuigan, 1938; guinea pigs, Bose and Mukerji, 1942), and on *heart-lung preparations.*

Clinical Standardization may be made quite conveniently by the change in the RT-T segment of the electrocardiogram, which is sensitive to a dosage change of about 25 per cent (H. Gold, 1944). Comparisons of the human, cat and frog method are reported by H. Gold *et al.*, 1941.

Frog-Heart Systolic Standstill Methods.—These determine the dose that must be injected into a lymph sac to produce the characteristic systolic arrest of the ventricle with dilated auricles, in a specified time, an hour (Famulener and Lyon), U.S.P. XI, or less (thirty to forty-five minutes, Gottlieb, 1908); or the time of arrest with a fixed dose (Focke, 1906). The method measures the true digitalis effect, and takes account of absorbability; but absorbability from the lymph sac does not necessarily parallel that from the alimentary tract. The time does not suffice for complete absorption (Schmiedeberg), so that the results are more variable than with other methods. When properly performed, however, with adequate numbers of animals, the average error can fall within 15 per cent. Dooley and Higley, 1923, advocated intramuscular injection.

Further difficulties arise from the *varying susceptibility* of different individuals. This is particularly great in frogs. It can be minimized by using a considerable number of animals and treating the results statistically, using the 50 per cent fatality as end point (L. C. Miller, Bliss and Braun, 1939). A part of the variability is due to differences which could be met by injection into the abdominal vein (F. Uhlmann, 1927); but it is chiefly inherent in the heart, for it occurs even with Straub hearts (Nyiri and DuBois, 1929). Frogs also show *seasonal variations*, the susceptibility being about 15 per cent higher in December than in June and July (Munch, 1931). This is one reason why control tests must be made with the standard specimens. The temperature must be carefully controlled not only during the test, but also for the prior day (Baker, 1912 and 1913). Alcohol (25 per cent) is not disturbing for frogs (Haskell, 1913).

Frog fatal dose methods determine the smallest dose which kills a given weight of animal in a given time regardless of the specific *cardiac action*. The most convenient is the twelve or twenty-four hour frog method (suggested by Cushny, and elaborated by Houghton, 1898; being the first commercial bio-assay process). They give more consistent results than the short time methods (L. C. Miller, 1944), but they may involve noncardiac constituents. The same precautions must be observed as for the systolic standstill methods. The M.F.D. of digitalis averages about 1.5 mg. per Gm. of frog.

The fatal dose for guinea pigs has also been used (Reed and Vanderkleed, 1914), and gives consistent results, but is open to the objection of nonspecificity. The M.F.D. of digitalis is from 0.06 to 0.1 Gm. per 240 Gm. of pig (Reed). Age, sex and weight are unimportant; but there are considerable individual and marked seasonal variations, and the food also has an influence (Vanderkleed and Pittenger, 1913; Haskel, 1913).

The fatal dose for goldfish was proposed by Pittenger and Vanderkleed, 1915, but is also nonspecific.

Pigeon Emesis Method.—The dose required to produce vomiting in pigeons correlates well with the clinical therapeutic and emetic potency (Hanzlik and Stockton, 1929). The results are comparable with those of the cat and frog method, provided sufficient animals are used (Burn, 1930). It can also be used for *ergot* (Lieb and Mulinos, 1934). Haag and Woodley, 1934, proposed intravenous injection, analogous to the cat method.

The sassy-wood ordeal of the West African natives is an assay directed to the suspect rather then to the drug. A decoction of erythrophleum is administered: vomiting with recovery establishes innocence; absence of vomiting, guilt. It has been suggested that the fear of the guilt serves to inhibit emesis (G. W. Harley, 1941).

Embryonic chick heart appears to furnish an ideal method of directly evaluating the specific cardiac action that is used in therapeutics, by the sharply defined time of appearance of A-V block without regard to absorption (Paff, 1939; R. A. Lehman and Paff, 1942). It is especially convenient for appraising relations of constitution and potency (R. A. Lehman, 1946). The material is always universally obtainable, which is an important advantage.

Excised or perfused frog hearts have been used mainly in scientific investigations (Schmiedeberg, 1910; Hartung, 1912; Gros, 1913; Straub; Santesson, 1915), as also excised sinus pieces (Mansfeld and Horn, 1928). They are not very practical.

The isolated papillary muscle of cat heart has been used by Cattell and Gold, 1941, especially for quantitative comparisons of the therapeutic concentration (increased contractile force) and toxicity (irregularity). This ratio was found similar for ouabain, digitoxin, and the lana glycosides.

Daphnia, a small crustacean, shows cardiac phenomena that reflect the digitalis potency (Viehoffer), but it is questionable how far its pharmacology corresponds to that of vertebrates.

Colorimetric Assay.—A chemical colorimetric method (Bell and Krantz) with an alkaline picrate solution, similar to the creatinine reaction, gives results that may approximate those of the cat method, both for digitalis and strophanthus (Knudsen and Dresbach, 1923), but it is not reliable (Vos and Welsh, 1945; Danow *et al.*, 1946).

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BARIUM

This stimulates all muscle, striped, unstriped and cardiac, irrespective of innervation. It is mutually antagonistic with all muscular depressants, regardless of whether these act on the receptive or on the responsive mechanism. Unlike the other elements of its group, Ca and Sr, barium is very toxic. Its chief effects resemble those of the digitalis group: it produces a similar action on the cardiac muscle; a strong vasoconstriction by direct stimulation of the arterial muscle (occurring therefore after apocodeine, Dixon, 1903); violent stimulation of peristalsis, even on intravenous injection; and stimulation and later paralysis of the central nervous system. It also produces local irritation, and is inimical to the lower forms of life such as yeast cells. The soluble barium salts, and the carbonate and sulfide, are sufficiently absorbed from the alimentary canal to produce the fatal effects. The sulfate, which is used in roentgen work, is insoluble and nontoxic; and sodium or magnesium sulfate are antidotes for barium poisoning. Barium is but little used in therapeutics, for fear of toxic effects.

Cardiac Action.—A. S. Cohn and Levine, 1925, reported that barium chloride (30 mg., ½ grain, by mouth, three or four times per day) suppressed permanently the syncopal heart block attacks of the Stokes-Adams syndrome, and it was also tried in angina pectoris (Levine, White). Others, however, failed to obtain good results (F. Parsonnet and Hyman, 1930) owing perhaps to the difference in the sulfate income?) and it has been abandoned, especially as the ordinary dosage may produce dangerous irregularities (Strouss and Meyer, 1928; McMillan and Wolferth, 1929).

Experimentally it acts like digitalis, increasing the excitability of the cardiac muscle and the force of the contractions (Wertheimer and Boulet, 1911). The rate is slowed even after atropine, so that this effect is muscular (Filippi). Slow intravenous injection of 8 mg. or more of barium chloride per kilogram, into dogs, produces extrasystoles and sharp rise of blood pressure, then ventricular fibrillation or tachycardia, and other irregularities. These are prevented or removed by inhalation of 20 per cent of CO_2 in oxygen, and less effectively by quinine. Sodium sulfate intravenously sometimes confers partial protection (Friedberg and Levinson, 1931; P. K. Smith, Winkler and Hoff, 1940). *Excised papillary muscle* of cat does not show the sustained systolic force characteristic of true digitalis action (S. Krop, 1944). Intracardiac application causes systolic arrest; dilute solutions, or exocardiac application, produce diastolic arrest, just as does digitalis (Poulsson, 1910; Werschinin, 1911; Delcorde-Weyland, 1913). The effects in complete heart block are similar to those of calcium (van Egmond, 1913). Whole auricles and ventricular segments of *turtle heart* show increased rhythmicity; contractility is usually depressed, excitability but little changed (Wedd and Blair, 1945).

Arterial Muscle.—The high rise of blood pressure under barium is due mainly to vasoconstriction. The effect is directly on the arterial muscle, and involves all arteries, regardless of their innervation (Cow, 1911). This might suggest its use in pulmonary hemorrhage, the lung vessels being strongly constricted (Berezin, 1914). However, the increase of the general blood pressure more than offsets the local constriction, so that the bleeding becomes more profuse (E. Frey, 1909). The liver veins are constricted in the guinea pig, not in the frog (Berezin, 1914).

Intestines.—Barium chloride produces violent peristalsis, culminating in intestinal spasm, which may be removed by magnesium (Sollmann and Rademaekers, 1925). The purgative effect may also be produced by intravenous injection in dogs (3 mg. per Kg.); but 7 to 8 mg. are rapidly fatal by the circulatory effects, without purgation. Rabbits are not purged by any dose although 18 mg. per Kg is fatal (Chistoni, 1918). The intravenous injection of 0.5 to 1.25 Gm. was used on horses to remove tympanites; but there were so many fatalities that it was generally abandoned (Dieckerhoff, 1895). The barium contraction of frog's intestine may be completely antagonized by epinephrine or pilocarpine (Roth, 1923).

Bronchial muscle is also constricted (Trendelenburg, 1912; Titone, 1913; Baehr and Pick, 1913).

Gallbladder.—The isolated organ is constricted (Lieb and McWhorter, 1915).

Salivary Secretion.—Intravenous injection of 5 to 10 mg. of barium chloride per kilogram into dogs or cats increases the flow of submaxillary saliva, resembling the response to chorda tympani stimulation, which is abolished by atropine. The secretion is accompanied by diminished blood flow through the gland, notwithstanding the rise of blood pressure. The contractile mechanism is not involved (Stavraky, 1932).

Skeletal Muscle.—Barium has two distinct actions on frog's gastrocnemius muscle (Zoethout, 1919): (*a*) Direct stimulation, persisting as long as the muscle remains in the solution. This requires the presence of Na ions, and is therefore abolished by isotonic sugar solution. (*b*) Contact irritability, seen only when the muscle is immersed or removed from the solution, being produced by the inward or outward passage of Ba ions. It is antagonized by certain Na salts. Both actions are antagonized by K, Ca and Mg ions, and by procaine or strychnine. Immersion of the muscle in barium chloride solution, 1:1000, produces rapid tremor and gradual rise of tonus. In the progress of nerve degeneration following section of the sciatic, the tremor response disappears much earlier than the tonus response; but the latter also fails when acetylcholine, nicotine and potassium chloride are still effective. Fuehner, 1926, attributed the barium effect to displacement of calcium from the motor nerve-endings.

Fowl's Muscle.—Injection of $BaCl_2$ produces only increase of muscular tonus in the normal leg, but after denervation it causes a strong contraction. The degenerating muscle has therefore become more susceptible to Ba. A similar result can be secured by preliminary injection of nicotine. Curare does not influence this contraction, indicating that Ba acts more peripherally than curare, nicotine or physostigmine.

Cerebral Stimulation.—Direct application of barium salts to the cerebral cortex stimulates the white matter, and increases the irritability of the gray matter (Maxwell, 1906)

Hematopoiesis is stimulated in rabbits by small doses; toxic doses are hemolytic (Zolezzi and Stazzi, 1939).

Excretion.—The main channel is by the intestine, only traces appearing in the urine even after parenteral administration (G. M. Meyer, 1909). A small amount may be deposited in the bones. Barium lessens the elimination of uric acid (Abl, 1913).

Mechanism of Action.—The effects of barium are perhaps due to the precipitation of a *film of colloidal barium sulfate*, which would modify the permeability of cells analogous to anaphylaxis (Lumière). Kundel suggested *deprivation of sulfate ions*, and Januschka thought to confirm this by the observation that a frog heart poisoned by barium can be restored by sodium sulfate, but not by phosphate or oxalate, although these are barium precipitants. However, Hermann, 1932, found that this is explained simply by the higher solubility of barium phosphate and oxalate, and that barium can be detoxified by less than the chemical equivalent of sulfate, so that the restoration does not leave any free sulfate ions.

Roentgenology.—The insoluble $BaSO_4$ is used in x-ray diagnosis. It is tasteless, inexpensive, and does not delay the gastric movements, as does Bismuth.

Barium Sulfate, U.S.P. (the title should never be abbreviated, to avoid confusion with the poisonous sulfide or sulfite), is nontoxic. For roentgen examination of the stomach, 300 Gm. are administered, suspended in 400 cc. of water; for the colon, 750 Gm., suspended in 1500 cc. of water, by enema (N.N.R.).

Toxicology.—Barium poisoning arises from the use of the barium carbonate as rat poison (1:4 of corn meal, made into a dough with water; Holsendorf, 1937). Mistakes have occurred by dispensing the sulfide instead of the sulfate for radiologic use. The sulfide is also available in depilatories. A. S. Allen, 1943, reported mass poisoning by the use of table salt containing up to 25 per cent of barium. Barium determination in atmospheric dust is described by H. Yagoda, 1944. Crawford, 1908, attributed "Loco poisoning" to the Ba contained in the western plants. This could not be confirmed (Alsberg, Black and Marsh, 1912).

The *symptoms of barium poisoning* consist in excessive salivation, vomiting, colic, violent diarrhea; convulsive tremors; slow hard pulse and high blood pressure; hemorrhages into the stomach, intestines and kidneys; muscular paralysis. Death occurs after a few hours or days. The fatal dose is probably 0.8 to 0.9 Gm. of the chloride. Barium carbonate and sulfide are also toxic, but act more slowly, and the sulfide requires relatively large doses (Stedem, 1920). The *treatment* consists in administering magnesium or sodium sulfate.

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SAPONINS (SAPOTOXINS; SAPO-GLYCOSIDES)

These comprise a series of related compounds, generally non-nitrogenous glycosides, which occur in many plants. The actions are somewhat related to soaps and bile salts. The saponins lower surface tension, and therefore concentrate on the surface. They form a solid and resistant pellicle, and when even very dilute watery saponin solutions (1:10,000) are shaken, each air bubble becomes coated with this tough surface film, producing a persistent foam. When shaken with oil or powders, the saponin film prevents the droplets or fine particles from coalescing, so that permanent emulsions or suspensions are easily formed. Saponin tends to displace other substances or absorbates from the surfaces; for instance, it liberates rennin that has been absorbed by charcoal. In these ways the saponins tend to alter the permeability of the protoplasmic surface of cells, and are generally protoplasmic poisons. They have a particular affinity for cholesterol. They hemolyze blood cells, even in isotonic or hypertonic salt solutions.

Fish are killed by high dilutions (1:200,000). Saponin has been used to kill *snails*, in schistosomatous waters (C. Pinto, 1944). In *higher animals* they are but little absorbed, so that they act mainly as local irritants to the mucous membranes. A few, however, are absorbable and toxic, producing hemolysis; in large doses also degeneration of liver cells, followed by fibrosis. They have been administered to increase gastro-intestinal absorption, for instance, of insulin, but with doubtful results. Senega is used somewhat as nauseant and emetic. Sarsaparilla and guaiac were formerly employed as "alteratives" in syphilis. Quillaja (soap bark) and saponaria (soap root) are used technically for cleansing. "Merck's *Saponin Purissimum*" is prepared from saponaria.

Chemical Properties.—Many of the typical members of the group have the composition $C_nN_{2n-8}O_{10}$. They are glycosides and give a purple color with concentrated sulfuric acid. They are generally not attacked by animal enzymes. They have the characters of colloids: they do not dialyze; most are soluble in water, and are not precipitated by moderate amounts of alcohol; but they do not dissolve in pure alcohol or in fat solvents. Many are precipitated by saturation with neutral salts, especially ammonium sulfate; by basic lead acetate, and so forth. Some behave as acids, others are neutral. When heated with dilute mineral acids they are decomposed into sugars (differing for the individual saponins) and a *sapogenin*. Schmiedeberg calls these decomposition products "saponins," and all the original substances "sapotoxins." Others apply this name to the more toxic saponins (review, Kobert, 1914).

Occurrence.—Sapo-glycosides are widely distributed through the vegetable kingdom, occurring in at least 400 plants, belonging to 50 different families. They are probably formed in the leaves, but are found in all parts of the plants. The foaming is so conspicuous that many of these drugs have received suggestive popular names, soap bark, soap root, and the like. They are employed even by noncivilized peoples, for cleaning, and on account of their high toxicity to fish as fish poisons. Some cause poisoning of grazing stock (Vaccaria). *Ophiotoxin*, a definite principle isolated from snake venom, is believed to be closely related to the saponins (Faust). *Crocus* bulbs contain a saponin toxic to young animals, but not to old (Kobert, 1917).

Local Actions.—Most of the sapo-glycosides are irritant to *mucous membranes*. They have an *acrid taste* and provoke a flow of saliva (sialogogue action), nausea, vomiting and diarrhea. The gastric mucous membrane shows transient turgescence, with marked increase of mucus and moderate increase of fluid (Ivančevič and Kadruka, 1939). If snuffed, they cause sneezing; if injected hypodermically, they produce *subcutaneous inflammation.*

Therapeutic Uses.—Senega is used as nauseant expectorant, especially in chronic cough, and as emetic. Its nonabsorption constitutes an advantage. The emulsifying action determines the use of quillaja as detergent, especially for the cleansing of articles which are injured by alkalis. The use of quillaja in medicinal emulsions or for producing foam in soda water is not admissible.

Some of the less toxic saponins might be used for this purpose (Kobert, 1904), but they have not been sufficiently studied to be entirely safe.

Sarsaparilla, which owes its activity entirely to the sapotoxin or saponin which it contains, formerly enjoyed considerable reputation as an *alterative*. This is no longer accepted (H. C. Wood, Jr., 1916); if it possesses any action at all it is simply that of a mild nauseant and cathartic.

Saponin on Absorption.—It has been claimed that saponin (clinically, 0.1 to 0.2 Gm. of Merk's Saponin Puriss.) increases the absorption of sugar (Lasch and Brügel) and of a variety of drugs (Korfler, 1932) from the alimentary tract, but the evidence is not conclusive, as the differences lie within the natural variation (Petschacher and Nageeb, 1929), and reliable workers (Dingemanse and Laqueur, 1927) failed to obtain increase of insulin absorption.

Systemic Actions.—If sapo-glycosides are injected directly into the circulation they produce hemolysis, diuresis (B. MacCallum, 1905; Asher, 1908), and direct actions, especially on the central nervous system, which may be rapidly fatal. At first there are violent convulsions; then paralysis, especially of the respiratory center. The effect on fish is also paralytic. Rapid absorption through the gills makes even small doses effective. *Smaller doses given by the blood* cause especially *intestinal symptoms*, and death after several days by collapse. Why the symptoms are so largely intestinal is unexplained. Given subcutaneously, they produce these same symptoms, but much more slowly. If they are applied directly to skeletal or cardiac *muscle* or to nerve trunks, these lose their irritability at once, and if the solution is fairly strong (1 per cent), there is rigor. Saponins act on amebae, but apparently not on bacteria (Bacon and Marshall, 1906).

Effects on Circulation.—Intravenous injection of Merck's purified saponaria saponin into rabbits, 20 mg. per Kg., produces a slight rise of blood pressure; larger doses cause rapid fall with extreme cardiac dilatation. Perfusion of *rabbit's ear* gives vasodilatation and then edema. Dog's heart-lung preparations show dilatation of the coronary vessels. Excised *auricular segments* of rabbits react with depression, arrhythmia and arrest (Gottdenker, 1938). Nearly all saponins are toxic to the *frog heart* (I. Traube, 1919). The addition of saponin increases the toxicity of digitoxin for the frog heart (Postoiev, 1911).

Effects of Hemolysis.—Hemolysis liberates potassium and other toxic substances from the corpuscles (Gottlieb and Lefmann, 1907; W. H. Brown, and Loevenhart, 1913); but these are not concerned in the systemic saponin actions: the latter occur with doses which are not hemolytic; nor are the systemic saponin effects avoided by cholesterol, which prevents the hemolysis. Presumably the permeability of the nerve cells is directly affected by the saponin.

Poisoning.—Most sapo-glycosides are absorbed so poorly that they produce only local effects: gastroenteritis, vomiting, persistent diarrhea, and so forth. However, the violent local action may lead to corrosion and this to absorption (*f. i.*, with quillaja). Agrostemma, the common corn cockle (chemistry, Brandt, 1906) is absorbed fairly readily and thus produces systemic poisoning. This is important since its seed may be admixed with grain. The systemic symptoms agree with those of intravenous injection. The toxicity of various saponins is ten to a thousand times higher by vein than by mouth, and is generally (but not always) proportional to the hemolytic action. The liver affords some protection, but larger doses produce degeneration of the hepatic cells, followed by fibrosis (Ewart, 1931). Some saponins have different toxicity for different species. Certain vegetables, for instance, *spinach*, contain saponins which appear harmless for man (Kobert, 1914).

Experimental Saponin Anemia.—Injections of subethasl doses of saponins cause destruction of the erythrolcyte by an indirect action on hemoclastic organs, especially the spleen. The liberated iron is stored mainly in the spleen; if this has been removed, it is stored in the liver. The urinary iron is not increased; the fecal iron is (T. Fukui, 1926). Daily intravenous injection of the maximum tolerated dose of saponin into rats gradually reduces their erythrocytes and hemoglobin to half or less. When the injections are discontinued, there is little change for ten to twenty days; then regeneration sets in, with nearly complete recovery in another three weeks (Stohlman and Smith, 1934).

Hemolytic Action.—Saponins lake blood even in an isotonic medium. The phenomenon depends on their affinity for the lipoids of the cell envelope and stroma. It is prevented by the addition of cholesterol or other lipoids which combine with or bind the saponin.

Hemolytic Concentration.—The limital concentrations 1:400,000 to 1:10, vary enormously, but are characteristic for the different saponins (Kobert, 1914).

Phenomena of Laking.—Saponin hemolysis occurs in two stages, which are practically distinct: the liberation of hemoglobin; and increased permeability of the envelope (G. N. Stewart, 1899 to 1909; Woelfel, 1908). The latter occurs even in formaldehyde-fixed corpuscles. Saponin does not cause the complete disappearance of the stromata; bile salts do (Neuberg and Haendel, 1908). The hemolytic activity of different saponins has no relation to their effect on *surface tension* (Woodward and Alsberg, 1916).

The saponin acts chiefly, if not solely, on the envelope, presumably on its cholesterol. The quantity of saponin or sodium oleate required for hemolysis is similar to the quantity required to cover the surface of the cell with a monomolecular layer. Smaller quantities sensitize to other hemolytic agents (E. Gorter, 1937). The electron microscope shows that the erythrocyte is enclosed in a membrane consisting of a framework of long protein threads in which cholesterol and lecithin are imbedded. Saponins precipitate cholesterol, forming definite crystalline compounds (Windaus, 1923). This combination so disorganizes the membrane that the hemoglobin escapes (J. Schmidt-Thomé, 1942).

Protective Action of Cholesterol.—Hemolysis may be prevented by adding cholesterol to the erythrocyte suspension before the saponin (Ransom, 1901). The protective action of *serum* is due chiefly to its cholesterol (Laube, 1911; E. Ponder, 1944). Pure lecithin does not protect. Cholesterol also protects the erythrocytes against toluidine compounds (Hildebrandt, 1911), sodium oleate, immune serum hemolysin, cobra lysin and some bacterial lysins, but not against some other hemolytic agents; for instance, the resistance of the blood of different animals varies inversely for saponin and water laking (Rywosch, 1911). The cholesterol protection does not extend to the central saponin actions. Cholesterol protects the heart against digitoxin, but not against all digitaloids (Karanlow, 1912). It antagonizes the systemic toxicity as well as the hemolytic action of sodium oleate (Klotz and Bothwell, 1915).

Acquired Resistance.—Repeated injections of saponin and other hemolytic agents raise the general resistance of the corpuscles (Kobert; R. Weil, 1910; contradicted by Kagan, 1913). No true antibodies occur. Prolonged saponin feeding increases the resistance, both of the corpuscles proper and of the serum (Alsberg and Smith, 1914). A similar increase of resistance occurs also in certain diseases in which hemolytic poisons are probably produced, *f. i.*, in syphilis, advanced cancer, and so forth. (Weil; McNeil, 1910).

Mixed Hemolysis.—Fuehner and Greb, 1912, found that the combination of various hemolytic agents (aliphatic, alkaloidal and glucosidal) gave complex results; the summation of the effects being sometimes simple, excessive or deficient. Saponin hemolyis is powerfully accelerated by proflavine and by 9-aminoacridine (H. B. Collier, 1945). The hemolytic action of watery solution of saponin is rapidly destroyed by the addition of *fluorescent substances*, eosin and erythrosin (Noguchi, 1906). Infusion of *tea* also has an inhibiting effect on saponin hemolysis; this has been proposed as a test for genuine tea (Maggiora and Ferron, 1914); but is probably due merely to the tannin.

Preparations.—*Sarsaparilla*, U.S.P., is the dried root of Smilax species. The Jamica variety contains a single saponin glucoside, "sarsasaponin" (Power and Salway, 1914). The *Fluidextract* is given in a dose of 2 cc., 30 minims, and is an ingredient of the *Compound Sarsaparilla Syrup*, used as an aromatic vehicle, especially for iodides. *Caulophyllum* (Blue Cohosh), the rhizome and roots of Caulophyllum thalictroides (chemistry, Power and Salway, 1913), is used as diuretic, emmenagogue and anthelmintic (see article under Nicotine and Ergot). Dose, 0.3 to 2 Gm., 5 to 30 grains. *Guaiac Wood* (Guaiaci Lignum), the heart wood of Guaiacum officinale or sanctum, contains 20 to 25 per cent of resin and some saponin (a trace of the latter is also contained in the Resin). There is some reason to believe the saponin is the bearer of the nauseant and purgative action. Guaiac, an almost obsolete remedy for syphilis, gout, rheumatism, tuberculosis, and so on, was introduced soon after the discovery of America, about 1501-1503. Nicholaus Pohl, 1517, stated that it had cured 3000 Spaniards. Its popularity was proclaimed in a famous pamphlet of Ulrich von Hutten, 1519. It was still strongly endorsed by Boerhaave (1668–1738), who wrote that "it will act as a purge, reaching places that mercury cannot reach, and there dissolve the poison." As early as 1538 Ruiz Diaz de Isla gave the credit to the associated regimen, and indeed von Hutten had some suspicion in this direction. *Guaiac Resin*, obtained from Guaiac Wood, contains a number of resinous acids, especially guaiaconic acid, which is colored blue by oxidation. This is inhibited by many anticatalytic agents; hydroquinone, epinephrine, gallic acid and cyanide are especially effective (E. Baur and Brunnschweiler, 1941). Dose, 0.3 to 1 Gm., 5 to 15 grains. The resin is commonly used as a reagent for oxidative ferments. Schaer, 1913, found the best results with resin extracted from the wood by chloroform; then the natural resin; then alcoholic extract of the wood. Solutions lose their sensitiveness with age. *Quillaja* (Soap Bark) is the dried inner bark of Quillaja Saponaria. Dose, 0.06 to 0.2 Gm., 1 to 3 grains. *Saponaria* (Soap Root) consists of the root or leaves of Saponaria officinalis. The dried powder contains 30 to 40 per cent of saponin. *Senega*, the dried roots of Polygala Senega, is given in a dose of 0.4 to 0.8 Gm., 6 to 12 grains. *Githagin*, a saponin glucoside from the seeds of *Agrostemma* githago, is readily absorbed, the seeds causing serious poisoning. Intraperitoneal injections into guinea pigs produce multiple internal hemorrhages in a few hours. Sublethal doses impair the adrenals (Buu-Hoi *et al.*, 1944).

The pharmacology of *horse chestnut saponin* is described by H. Hindemith, 1943.

SOLANINE

The glucosidal alkaloids, solanine, solaneine, and solanidine, which occur in plants of the potato genus (Solanum nigrum, dulcamara, tuberosum [Potato], Carolinense and Tomato), produce typical sapotoxin actions. Solanine splits into sugar and solanidine. The solanine literature is reviewed by Meyer and Schmiedeberg, 1895. In certain species, particularly in S. dulcamara, the solanine alkaloids are associated with a small quantity of atropine-like alkaloid and with a saponin (dulcamarin).

Potato (*Solanum Tuberosum*).—The toxic principles are distributed throughout the plant, but only small quantities are found in the pulp of the tuber—too small to produce any action. The quantity is larger in the peel, and especially in young and in sprouting potatoes and in the green-colored skin and flesh; but it is not increased by storage. The amount in potato is ordinarily too small to be harmful (less than 0.01 per cent), and it was doubted whether "potato poisoning" could be due to solanine (Droste, 1915). However, under conditions that are not understood the solanine may occasionally rise to four or five times this quantity. Since 0.2 Gm of isolated solanine provokes untoward symptoms in man, potatoes containing this high quantity of solanine are poisonous, as shown in the outbreaks of Leipzig (Rothe, 1919) and Glasgow (Harris and Cockburn, 1918). In both, the suspected potatoes contained over 0.4 Gm. of solanine per kilogram. The symptoms pointed to gastro-intestinal irritation: vomiting, diarrhea, colic, headache, depression, and the like. They may be severe, but no fatalities have been recorded (Pohl, 1924).

Solanum dulcamara ("*Bittersweet*") has been used as a nauseant (*Dose*, 4 cc. of the fluidextract, prepared from the young branches). The berries of *Solanum Carolinense* were used in epilepsy (dose, 4 cc. of the fluidextract), generally with bromides, so that the effects are difficult to judge. *Tulip bulbs* contain an alkaloid, tulipine, closely related to solanine and colchicine (Kobert, 1917).

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COLCHICUM

Colchicum (Meadow Saffron), and its active alkaloid colchicine, a phenanthrene derivative, are used empirically to avert or mitigate acute attacks of gout. Colchicine has a remarkable effect on cell division, arresting it in metaphase, even when it is administered to intact animals. Toxic doses produce a characteristic late gastro-intestinal irritation, even on hypodermic administration. The vomiting, purging and intestinal congestion may be so violent as to lead to fatal collapse, so that the plant (all parts) is of toxicologic importance. The other actions are relatively insignificant.

Therapeutic Use in Gout.—Colchicum and colchicine are credited with prompt and sometimes dramatic effects on acute gouty attacks, relieving the pain in one or two hours, the heat and swelling subsiding soon after, and the attack ending in a few days instead of weeks. It must be used early and rather freely, in doses large enough to produce some diarrhea. It does not prevent recurrence, soon loses its efficiency and is often unsuccessful. It gives little or no relief in nongouty arthritis (Lockie, 1939). It prevents or diminishes the experimental inflammatory reactions of local joint anaphylaxis (A. Beck, 1932). The effect is probably connected with its irritative *dilator* action on capillaries; but it also causes characteristic changes in the blood picture, leukopenia followed by leukocytosis. These reactions resemble those of nonspecific protein injection.

Administration.—Tincture of Colchicum Seed may be given in divided doses, 0.5 cc., 8 minims, every three hours (advantageously with an equal quantity of magnesium carbonate or sodium salicylate), until a therapeutic response or slight gastro-intestinal disturbance and weakness occur. Some disturbance of digestion and soft stools are the rule, and in susceptible patients there may be considerable purging and faintness. This may be lessened by atropine, but if possible should be avoided by proper dosage. A single large dose, 2 to 5 cc., ½ to 1 ʒ of tincture, acts more promptly, but may cause severe nausea, diarrhea and great muscle weakness. Prolonged administration is generally harmful and therefore inadvisable. *Colchicine* permits more definite dosage. It may be given, 0.5 to 1 mg., 1/120 to 1/60 grain, three times daily, for one or at most two days. This usually causes considerable diarrhea, beginning on the second day, and with its appearance the drug should be discontinued. The stools remain loose for another day.

Historical.—The toxic properties of colchicum are mentioned by Dioscorides. It was used against gout or rheumatism by the Arabian school (sixteenth century), and since then in domestic practice; but was abandoned in regular practice on account of its poisonous action, till it was reintroduced by Stoerck, 1763. The weakness of the earlier pharmacologic explanations is reflected in the references of S. Loewe, 1920.

Metabolism.—The *urine* secretion is sometimes slightly increased, sometimes greatly diminished, probably depending on the catharsis. The statements as to uric acid and urea (*e. g.*, Noel Paton, 1886; Maurel and Arnaud, 1910; Abl, 1913) are so contradictory that they can have little importance. With the modern methods, Denis, 1915, found neither increased elimination of urates in the urine, nor diminished concentration in the blood. The *bile* flow is slightly increased (Kionka, 1906).

Leukocytes.—Hypodermic injection of colchicine, 3 mg. per Kg., into rabbits, produces leukopenia lasting about an hour and followed in two to six hours by remarkable leukocytosis. The polymorphous cells may attain a maximum of two to five times the normal in ten to twenty-four hours. The effect may persist as long as eight days; with repeated administration it is cumulative (Dixon and Malden, 1908). The *blood coagulability* is accelerated during the leukopenic stage, and retarded with the leukocytosis (Loicq, 1937).

Mitogenetic Activity.—Administration of colchicine (0.2 mg. per 100 Gm., hypodermically, for mice) arrests mitotic division of cells in general in the metaphase (Lits, 1934; Brues and Cohen, 1936; E. Allen, Smith and Gardner, 1936; Ludford, 1937). This effect occurs also in *plant cells*, suppressing spindle fiber formation and inhibiting the separation of the cell after the division of the chromosomes, so that the number of chromosomes is doubled (polyploidy). If the drug is now removed, the nucleus divides normally, producing plants in which the double number of chromosomes is reproduced indefinitely, and this is transmitted to the seed and descendant (Nebel and Ruttle, 1938; R. I. Walkers, 1938).

With *chick embryos* it results in retardation of growth and various abnormalities (Paff, 1939; Angel and Tallemand, 1940). The effect on mitosis is observable on tissue cultures of embryonic chick heart, but these are killed by concentrations above 1:1,000,000 (Törö and Vadász, 1939). It is useful *to demonstrate the active growth stimulation* of genital tissue by theelin (E. Allen, Smith and Gardner, 1937; E. Shorr and Cohen, 1941, vaginal suppository of 1 to 3 mg.), or by androgenic hormone, thyroid stimulation by pituitary hormone, and so on (Fleischmann, 1938). The arrest of mitosis in metaphase leads to the death and destruction of normal tissues with rapid cell division (Clearkin, 1937).

Frog ova fertilized with *sperm* exposed to 0.04 per cent for three hours show various developmental anomalies (T. S. Hall, 1946). Local application of colchicine to normal human or rabbit *skin* results in transitory alterations of the nuclear pattern of the epidermis, similarly to podophyllin (J. S. King and Sullivan, 1946).

Colchicine checks the growth of certain mouse *tumors* (Lits and Kirschbaum, 1938); but curative results were not obtainable with tolerated doses (E. Schairer, 1940). The tumors recur except with doses just short of lethal, which produce vascular injury (R. J. Ludford, 1945). In other types it appears unsuccessful. In one form (sarcoma S37) it does not inhibit the growth of transplants in the animal, but it checks tissue cultures of the tumor from the treated animals (Clearkin, 1937). Rat carcinoma is rapidly destroyed by local injection of water, fifteen hours after administering colchicine (Guyer and Claus, 1940). Doses approaching to toxic cause hemorrhages in tumors (but no more than with bacterial filtrates, Andremont, 1940) with decrease of their ascorbic acid content and metabolism. They also decrease the ascorbic acid content, but not the metabolism, of the liver and intestines (Boyland and Boyland, 1937). *Plant tumors* are killed by brushing with a 2 per cent solution (N. A. Brown, 1942).

Mitosis effects identical with those of colchicine, including polyploidy, are produced by a whole series of derivatives and chemically related substances; by veratrine and sanguinarine; and by acenaphthene, α-methylnapthalene, α-nitronaphthalene, 3-5 dibromopyridine, and by apiol (C. F. Branch, 1942; Lettré and Fernholz, 1943).

The **symptoms of colchicum poisoning** set in only after three to six hours, even with large doses. They begin with burning and rawness in the mouth and throat, sensation of strangling, difficulty of swallowing, nausea, abdominal discomfort, followed by violent and uncontrollable vomiting and purging, colic and tenesmus, spasm of the bladder and great prostration. The stools are at first normal, but become dysenteric and bloody. They are not especially painful, but are exhausting, so that the patient passes into collapse, with the nervous and muscular symptoms of cholera. Death occurs in seven to thirty-six hours from exhaustion, consciousness being preserved nearly to the end; or by respiratory paralysis, with the patient unconscious and deeply cyanosed. The *fatal dose* varies; ½ ounce of the Tincture has been fatal. This would correspond to about 8 mg. of colchicine; but recovery has occurred from much larger doses, presumably with imperfect absorption. The *treatment* includes evacuation by emesis and catharsis, if necessary, and diuresis. Tannin is a chemical antidote, but not very effective. Opium and belladonna are given against the gastroenteritis, and the collapse is treated as usual. *Autopsy* reveals intense and often hemorrhagic congestion of the intestines, especially the lower portion.

Gastro-Intestinal Irritation.—The intense congestion and violent peristalisis occur even on parenteral administration, but this has no special significance, since the colchicine is excreted into the intestines (Speyer, 1870). The action is not directly on the muscle or its innervation, for excised intestine is depressed in tone and excursions by colchicine or oxydicolchicine (Fuehner and Rehbein, 1915). Rossbach, 1876, stated that the motor response to the intestinal vagus or splanchnic is not affected. Fuehner and Rehbein refer the entire action to irritative capillary vasodilatation analogous to the local actions elsewhere, and produced by contact with the drug, reaching the intestine directly or by excretion. They find this hyperemia of the stomach and intestines even with small doses. Lipps, 1920, confirmed the occurrence of hemorrhagic gastro-enteritis after hypodermic administration. He assumed that a capillary hyperemia occurs in other organs, including inflamed regions, and that this is the basis of the therapeutic results.

Local Action.—Strong solutions applied locally to the conjunctiva or subcutaneous tissue produce hyperemia, irritation and anesthesia.

The *central nervous system* is gradually paralyzed from below upward, partly directly and partly by the collapse.

Therapeutic doses exert no *appreciable direct effect on the circulation* (but the pulse may be somewhat slowed by the relief of the symptoms); *nor on the glands, striped muscles, or motor nerves* (Rossbach; Dixon and Malden). In *excised frog heart*, colchicine paralyzes the vagus endings (Jacobson, 1925). On *excised skeletal muscle*, it acts analogous to veratrine, causing higher and longer single twitch, and more rapid fatigue on rhythmic stimulation (Frey, 1923).

Explanation of the Delayed Action.—The long period before the symptoms appear cannot be materially shortened by increasing the dose (Schorff and Rossbach, 1896), or by intravenous injection. Colchicine itself has relatively little effect on frogs; but its toxicity for these can be increased four hundred times by raising their temperature from 19° to 30° C. (Sanno, 1911). This corresponds strikingly with the observation of Fuehner and Wagner, 1932, that colchicine is four hundred times more toxic to mice than to frogs at room temperature; *i. e.*, heated frogs react to colchicine as warm-blooded animals.

Jacobj, 1890, concluded that it is not the colchicine itself which produces the symptoms, but an oxidation product—oxydicolchicine—which is formed from it in the mammalian organism—even by circulating it through excised organs—but does not seem to be capable of formation in the frog's at a low temperature. Once formed, whether in the above manner or artificially by the action of ozone, it is toxic to frogs also.

Bio-Assay.—The toxicity to mice or heated frogs may be used (Fuehner, 1910).

Colchicine Derivatives.—The structure of colchicine was established by Zeisel, 1888, and Windaus (Fuehner, 1913). By treatment with acids, a methyl group is split off and replaced by OH, yielding *colchiceine*. This and various other derivatives were studied pharmacologically by Fuehner, 1913. The relative toxicity for various animals shows interesting differences.

PREPARATIONS.—***Colchicum Seed Tincture,** U.S.P., represents 10 per cent of the dried, ripe seed of Colchicum autumnale, and contains 0.04 per cent of colchiceine. Dose, 0.3 to 2 cc., 5 to 30 minims. *Colchicine*, U.S.P., is sol. in water (1:25) and in alcohol. Average dose, 0.5 mg., $\frac{1}{120}$ grain. *Colchicine Tablets*, U.S.P.; usual size, 0.5 mg.

ACONITE

Aconite (grown in gardens as "Monkshood" and "Venus' chariot") owes its activity to the rather unstable alkaloid, aconitine. This is a peripheral and central stimulant and depressant. Locally, the peculiar stimulation (tingling) and anesthesia (numbness) of sensory nerves, without inflammatory phenomena, is used against neuralgic and rheumatic pains, but has no advantage over capsicum. Systemically, therapeutic doses produce mainly a slowing of the heart (central vagus stimulation) which has been employed in sthenic fevers. Larger doses are highly toxic, producing great general depressions, extreme irregularity of the heart (mainly by direct action on the cardiac muscle), and death by arrest of the respiration or heart.

It is doubtful whether the systemic use of aconite is advisable. Effective doses are practically toxic, and safe doses are practically ineffective. The difficulty is increased by the variability and instability of aconite preparations.

The tincture, the most commonly used preparation, contains 10 per cent of aconite, U.S.P. (Formerly the strength was 35 per cent, U.S.P. These differences must be remembered in connection with older clinical papers.)

Historical.—The toxic properties of aconite were known to the ancients; however, there is considerable confusion, since the Roman poets used "Aconite" to denote vegetable poisons generally (Fleming). Various species, most of which are toxic, grow in different parts of the world. They were used as arrow poisons by the ancient Chinese and Gauls. The therapeutic use dates from Anton Stoerck ("Observations on the Use of Conium, Stramonium, Aconite, and Colchicum," 1763), who described the tingling without reddening or corrosion, the salivation and sweating, and proposed its use against rheumatic and neuralgic pain, and for "dissipating" swellings and healing ulcers. Alexander Fleming, of Edinburgh, 1845, published a comprehensive experimental and clinical "inquiry" of Aconitum Napellus, which is still a good model for therapeutic observation. Aconite is a favorite remedy of the homeopathic school. Several species are used in China as local anesthetic (H. P. Chu, 1927).

Chemistry of Aconitine.—The chief active constituent of Aconitum Napellus is the alkaloid *aconitine*. It is the acetyl-benzoyl-ester of *aconine*, a base derived from quinoline (Ehrenberg and Purfürst). *It decomposes readily*, even on boiling, with water, into benzoyl aconine (picroaconitine, iso-aconitine), and this again into aconine (Freund and Beck, 1894). They have the same actions as aconitine, but picroaconitine is only about $\frac{1}{60}$ as potent as aconitine; aconine, $\frac{1}{2000}$. These and other decomposition products preexist in the drug, and are probably formed in its extraction and especially in the manufacture of the alkaloid. *Commercial "aconitines"* may represent mixtures of varying strength, some being a hundred times more active than others. Several fatal accidents, to which it gave rise, have led to the practical abandonment of the internal use of aconitine in therapeutics. *Other species of aconite* contain related alkaloids, with similar actions: pseudaconitine or nepaline; indaconitine; bikhaconitine; japaconitine, and so on. T. R. Fraser, 1873, showed that the effects of aconitine and pseudaconitine are qualitatively alike; but that aconitine acts much more on the heart, pseudaconitine on the respiration. He further reported in 1916 on some East Indian species.

Local Actions.—*In the mouth* even a small quantity of dilute solutions of aconite produces a peculiar warm and *tingling sensation*, a sour rather than bitter taste, followed by numbness and anesthesia. The lips, tongue and mucous membrane of the mouth and throat feel as if swollen. The flow of saliva is increased reflexly. The apparent irritation is not accompanied by redness, pain, objective swelling or other sign of inflammation. It is therefore purely sensory. Analogous effects—heat, tingling and succeeding numbness, without inflammation—are produced in any other situation to which the drug may be applied; and even on the systemic administration of large doses. From the *skin*, watery solutions are but slightly absorbed, and friction must be employed to secure the local effect. Oily solutions and ointments are absorbed readily.

Eye.—Fleming claimed that the application to one of the temples, or one side of the forehead, may produce more or less (temporary) *blindness* on that side. The *pupils* are then dilated, presumably to admit more light. The application to the conjunctiva constricts the pupils. In systemic poisoning, they are constricted until the final asphyxial dilatation.

Therapeutic use of the local action is made for the relief of toothache, neuralgia, migraine, rheumatic and other similar pain. For this purpose it may be employed by thorough friction of the tincture, undiluted or with the addition of 1 to 10 parts of soap liniment. This is probably as effective as the expensive Unguentum Aconitinae (2 per cent).

Fleming claimed that the internal use of the tincture is often more effective in neuralgia. He started with about 1 cc. of the U.S.P. tincture, three times daily, and increased the dosage until the full therapeutic effect (pulse of 54, lethargy, and so forth) was obtained.

The systemic effects of therapeutic doses consist mainly in more or less pronounced *slowing of the heart rate*, to 60 or 54 beats per minute, according to the dose and the susceptibility of the individual. The pulse is also softer and weaker, but remains regular as long as the dosage of slowing is not surpassed. The blood pressure falls slightly. The therapeutic slowing (often absent in anesthetized dogs) is due mainly to stimulation of the vagus center, for it is practically absent if the vagi have been divided (S. A. Matthews, 1897). The typical slowing, which occurs in one and one-half to two hours if the tincture has been taken by the mouth, is preceded by *subjective sensations* of evanescent warmth, and persistent numbness and *tingling*, beginning in the finger tips and extending along the arm, as the dosage is increased. The *respiration* is moderately slowed and more or less labored. With the full therapeutic dosage, the patient is weak, giddy, confused, lethargic and cold. These phenomena last for three to five hours and are as far as the therapeutic action should be carried. They are produced by doses corresponding to 0.15 to 0.3 Gm. of aconite (Fleming), *i. e.*, by 1.5 to 3 cc. (20 to 45 minims) of the 10 per cent U.S.P. tincture.

Sweating may occur, but is not constant. The *urine* is not increased. The *temperature* is not markedly affected by the therapeutic doses. *Digestion* and *peristalsis* are not disturbed. *There is no cumulative action.* The *vasomotor center* is not affected by nontoxic doses. Toxic doses, however, produce a maximal stimulation, more intense than can be obtained from stimulation of sensory nerves (Pilcher and Sollmann, 1915).

Inactive Tinctures.—Several observers have been unable to obtain effects on the pulse and blood pressure, from small and fairly large doses, in a variety of clinical conditions. These negative results are probably ascribable to inactive preparations of the drug, as with Robinson, 1915.

Therapeutic Uses.—The slowing of the circulation has been utilized in heart disease, in hypertension and in sthenic fevers, but is of doubtful value, especially in view of the total inefficiency of the dose ordinarily given.

Sthenic Fevers.—In these it was supposed to "calm" the overactive heart and to promote the action of mild diaphoretic agents (spirits of niter, ammonium acetate, and so on). It is used in this way during the sthenic stage of acute fevers, especially in children, for the "abortion" of colds. According to Ringer, it is administered in small and frequent doses (3 to 5 drops of the 10 per cent tincture for adults, at first every fifteen minutes for two hours, then every hour, until the pulse returns to normal), and only for the first day of the fever, to avoid depression. It is difficult to judge its usefulness under such conditions.

Toxic doses increase the force and especially the rate of the heart, at the same time rendering it extremely arrhythmic. The beats may occur in groups, as with digitalis. The heart finally goes quite suddenly into delirium cordis, and stops. During the earlier stages of this action the blood pressure is extremely variable, according to the varying force of the heart, and the successive stimulation and depression of the vasomotor center. Toward the later stages, the pressure drops severely (Matthews, 1897; for further details of the interesting cardiac irregularities consult Fleming, p. 31; and Cushny, 1909). *Electrocardiograms*, in dogs, show ventricular tachycardia, fibrillation, flutter and death (J. B. Wolffe and Munch, 1934).

The cardiac effects are due partly to stimulation and depression of the vagus and accelerator mechanisms, but mainly to direct action on the cardiac muscle. The excitability of the latter is greatly increased, somewhat as with digitalis. The quickening occurs in the nerve-free heart of the embryonal chick; in mammals also it is seen after all the nerve endings in the heart have been paralyzed by apocodeine. With *isolated mammalian heart* (Hedbom-Langendorff) the initial effects are inconstant; the frequency is then enormously increased and the amplitude lessened below what is accounted for by the quickening (increased irritability and weakened muscle). Then follows a transient increase of amplitude (muscular stimulation), and sudden stoppage of the left ventricle (paralysis of automatic property). The right ventricle and the auricles make a few more contractions. Caffeine may start a few beats.

Perfusion of Medulla in Turtle.—Aconitine stimulates the cardio-inhibitory center (Bush, 1920).

The actions of aconite on the frog's heart are practically identical in the intact frog and in perfused excised heart. They are therefore peripheral. They consist in heightened irritability of the auricular, and especially of the ventricular, muscle; disturbed conduction; lessened contraction intensity, and finally paralysis. The successive effects are described as follows (Boehm, 1871; Fuehner, 1911). (1) *Preliminary slowing* is sometimes observed. It is probably due to stimulation of the vagus endings. (2) *Acceleration.*—Rather suddenly the beats become quickened and at first strengthened. The acceleration is attributed to heightened irritability of the cardiac muscle. The time of contraction and the refractory phase are shortened. (3) *Incoordination.*—Ventricular extrasystoles appear (even when the auricles are removed). The rate of the ventricle increases above that of the auricles, at first in a regular ratio. The combination of the two rates results in "periodic dissociation" or grouped beats. As the rate continues to increase, the contractions cannot be maintained regular, and become extremely incoordinated, resulting in the characteristic "*peristalsis*" of the heart muscle. This begins in the auricles, but soon extends to the ventricle. It consists in vermicular movements, in which the blood, instead of being propelled, is merely moved about in the heart. The localized contractions may lead to a mulberry appearance. Sometimes the contraction sequence is reversed so that the ventricular contraction initiates the auricular beat. These irregularities may alternate with periods of quite normal beats. The regular rhythm can often be restored by stimulating the accelerator nerve. (4) *Standstill.*—The extreme irregularity always passes off after a time, and is succeeded by slow and weak, but fairly regular, contractions, except that the ventricle beats much slower than the auricles. Eventually the ventricle stops relaxed, and then the auricles, usually rather suddenly. The peculiar heart "peristalsis" is the most delicate and characteristic *test for aconitine.* Fuehner, 1911, could detect 1/100 mg. in intact frogs and 1/1000 mg. in excised hearts. Similar effects are produced by the related delphinine. The digitalis group also produces peristalsis, but this is of short duration and followed by systolic standstill.

Respiration is progressively slowed in proportion to the dose (Fleming). It is labored, and the later stages become irregular. The slowing resembles that of vagus stimulation; but since it occurs also after section of the vagi (Boehm and Wartmann, 1873), it must be due to direct depression of the respiratory center, or perhaps to a cardiovascular reflex. It is characterized by prolonged expiratory pauses. Primary increase of respiration has been claimed, but it is small and inconstant, and probably due to other factors (Hartung, 1912).

The **temperature** falls in severe poisoning, by the collapse and consequent paralysis of heat regulation. The temperature of the animal falls and rises with the external temperature (Brunton and Cash, 1886).

Summation of Dosage.—The influence of this on temperature was studied by Cash, 1906. He found an imperfect summation of effect if the dose is repeated at sufficiently close interval. But if this exceeds two hours, the later doses may produce actually less effect, *i. e.*, the temperature may not fall so low as with the first dose. *Repeated administration* produces some tolerance in rabbits (Hartung, 1912).

Reflexes generally are diminished, on account of the sensory paralysis.

Skeletal Muscles and Motor Nerves.—Strong concentrations of aconitine at first stimulate and then paralyze the motor nerves peripherally. The stimulation is manifested by *fibrillary twitching,* occurring in muscle-nerve preparation, spontaneously or especially after stimulation of the nerve. The threshold of stimulation is lowered. The twitchings do not occur after curare, and must therefore be in the endings. They may be seen in living animals. The subsequent paralysis of the nerve, and eventually of the muscle substance, cannot occur during life, since the dose and the time required are greater than what would paralyze the heart (Hartung, 1911). The allied *delphinine* has been recommended as a substitute for curare in frog work (Schiller, 1904).

Infusoria and plants are also killed by aconite (Fleming).

Absorption and Excretion.—The absorption occurs readily from mucous membranes; alcoholic and oily solutions are absorbed from the skin. Lewin states that it is excreted promptly by the urine, feces, saliva and intestinal mucosa.

Symptoms of Aconite Poisoning in Man.—With large doses death may occur almost instantly, presumably by ventricular fibrillation. With moderately toxic doses, there is *tingling* in mouth, stomach and skin (the *most important diagnostic feature*); excessive salivation; nausea, retching, *vomiting* and *diarrhea* (the mechanism of the emesis is central; Eggleston and Hatcher, 1915) The burning passes into anesthesia. There is great restlessness. The *pulse* is slow and feeble, later arrhythmic and rapid. *Respiration* is dyspneic. There are muscular weakness, incoordination, vertigo. The *skin* is cold and livid. The *pupils* are first constricted, then dilated from the asphyxia and convulsions. The *intelligence* does not usually suffer, but there may be stupor and even unconsciousness. The *special senses and speech* may be impaired. *Convulsions* are common. *Death* may occur by heart paralysis or by paralysis of the respiratory center (the heart beating after death; Fleming). The symptoms may appear almost instantly, and are rarely delayed beyond an hour. In fatal poisoning death occurs usually in two to six hours. There are no constant *postmortem changes.* Severe symptoms follow from 5 cc. of the Tincture; 20 to 40 cc. may be fatal. For *treatment,* the common alkaloidal antidotes and evacuations should be employed. The symptomatic treatment should be mainly stimulating: warmth, ammonia, atropine. Artificial respiration may be life saving (Lewin, 1875). In extremis, cardiac stimulants (epinephrine) may be used intravenously.

Etiology.—*Accidental poisoning* from the fresh plants—which, as monkshood and the related larkspur, are common in gardens—as also from liniments, and so forth, is fairly frequent. On account of the small dose, the absence of postmortem signs, and the difficulty of chemical proof, aconitine was used for *suicide*. The use of the plant for *criminal poisoning* is widely spread in the East. The symptoms are so unmistakable—especially the tingling—that it has not found many users in civilized countries.

Variability and Instability.—Bio-assays show that the alcoholic tincture deteriorates materially within a year, and is practically inactive in three years after manufacture. The deterioration is said to be prevented by acidification (Swanson and Walters, 1923). Commercial tinctures were found by Haskell *et al.*, 1915, to vary 1000 per cent; commercial solid extracts differ even more widely, some being 5000 times more active than others (A. R. L. Dohme, 1918). It may be expected that there is now much less variation in the United States, since the bio-assay is compulsory.

Aconite, N.F. (Wolfsbane, Monkshood), the dried tuberous root of Aconitum Napellus, is frequently cultivated in gardens. All parts of the plant are poisonous. Dose, 60 mg., 1 grain. *Aconite Tincture*, N.F., 10 per cent; dose, 0.6 cc., 10 minims. The tinctures of the older pharmacopoeias were of different strength: 35 per cent in U.S.P. until 1890; 5 per cent in B.P. until 1915. Various species of *Larkspur* seed (*Delphinium*) contain alkaloids closely related to aconitine, both chemically and pharmacologically, and have been used for the destruction of body parasites since antiquity. They have often caused poisoning in children, and in cattle and horses (Marsh and Clawson, 1916). *Staphisagriae Semina* (Stavesacre), the ripe seeds of Delphinium Staphisagria, are used locally against pediculosis capitis or pubis, in the form of the 10 per cent Ointment, or as the Fluidextract diluted with 8 to 10 parts of soap liniment or bay rum. It must not be used if the skin is broken. It causes considerable local irritation, and sometimes eczema (Lewin)

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VERATRINE (CEVADINE)

Various species of veratrum (green and white hellebore), cevadilla, zygadenus and other liliaceous plants contain mixtures of related alkaloids. These are esters of definite bases and acids, related to aconitine both in structure and action, to digitalis and to solanum alkaloids. They produce multiple effects to which a common key has not yet been found (review, O. Krayer and Acheson, 1946). "*Verat'rine*" is a mixture of alkaloids, extracted from "cevadilla" seeds, which owes its activity mainly to cevadine. It must not be confused with veratrum and its active constituent, protoveratrine, since their actions differ in important particulars. Veratrine produces a characteristic prolongation of muscular contraction of considerable physiologic interest. Therapeutically it is rarely used as a counterirritant in neuralgic conditions, and as a parasiticide against pediculi capitis.

The composition of veratrine was studied especially by Wright and Luff, 1878, and Allen, 1896. *The principal* constituent, both in quantity and action, is the crystalline *cevadine*, the methylcrotonic ester of the base cevine. It is *not* present in Veratrum album; traces are said to occur in Veratrum viride, but this is doubtful. The second important alkaloid of "veratrine" is the amorphous *veratridine*, the veratric ester of verine. This is the "veratrine of Wright and Luff." Its effects agree qualitatively with those of cevadine (Boehm and Lissauer). The commercial "veratrine" contains small quantities of at least three other alkaloids: *cevadiline*, *sabadine* and *sabadinine*. All these are but weakly active. *Germerine*, an alkaloid isolated from Veratrum album by Poethke, 1937, acts much like protoveratrine and veratrine, but also produces some sympathetic stimulation by a peripheral action which is sensitized by cocaine and by ergotamine (Haas, 1938).

The action on striped muscle consists in a characteristic modification, so that it responds by a prolonged contraction to a single stimulus. The nature of this contracture is in dispute. It is actively maintained, and is not a tetanus, since electrograms do not show rhythmic oscillations (de Boer, 1927). It is a special type of contraction, which occurs normally in fetal muscle and in the extrinsic eye muscles of mammals, and is probably identical with the "Tiegel contracture" evoked in excitable muscle to a supermaximal stimulus, and also evoked in special conditions, including drugs such as veratrine, and less typically by formaldehyde, glycerol, and so forth. Analogous changes are shown by nerve, but this is not essential to the veratrine contractures, for it occurs also in curarized muscle (*reviews of muscle contracture:* H. S. Gasser, 1930; Bremer, 1932).

The veratrine contracture is now conceived of as repetitive responses, both of the muscle and the nerve, which outlast the stimulus (Krayer and Acheson, 1946), probably by sensitization of the muscle to the potassium ions liberated by stimulation of the nerve (G. Coppée, 1942).

Veratrine in Myasthenia.—Kroll, 1934, claimed beneficial effects, especially when it was administered in conjunction with ephedrine. It may be doubted whether safe doses would have appreciable effects.

Phenomena in Intact Frogs.—When an animal, and especially a frog, has been poisoned with veratrine, it shows striking peculiarities in its movements. It can contract its muscles with ordinary quickness, but it can not recover its former position for some time (v. Bezold, 1866).

Form of the Muscle Curve.—The reason for this behavior can be demonstrated on isolated muscle. Frogs are most convenient for this purpose, but identical phenomena occur in mammalian muscle (Quagiariello, 1913): if a veratrinized muscle is stimulated with a single shock, the ascent of the muscle curve is as abrupt as usual, but the relaxation is greatly prolonged. The muscle remains in what appears to be complete tetanus, but further analysis reveals that the phenomenon is not an ordinary tetanus.

The Contracture Is Not an Ordinary Tetanus.—If the nerve of a normal muscle-nerve preparation is laid on the veratrine muscle, a single shock sent into the latter causes a single twitch of the normal muscle, and not a tetanus as would be the case if the veratrine muscle were in ordinary tetanus (Fick and Boehm, 1872). However, if the veratrine stimulated the whole length of the muscle fibers at once (in contrast to ordinary tetanus, where the stimulation originates from the motor end plates), there would be no difference of potential, and therefore the nerve of the second muscle would not be stimulated, once the shortening of the veratrine muscle is completed. It is therefore not excluded that the veratrine contracture may be a tetanus, but with the site of stimulus production distributed throughout the length of the muscle. Observations on the development of the contracture in dilute solutions point in this direction, a single stimulus producing first a normal contracture, then fibrillary twitching, and finally contracture even in the absence of extraneous stimulation (Lamm, 1912). Cathode ray oscillograms show multiple rhythms. As these do not occur in the motor nerve, they must arise in or beneath the end plates. It has been suggested that these may be interpreted as ganglion cells, which are not normally automatic, but may be sensitized by veratrine (Eichler, 1938). High concentrations of veratrine paralyze all forms of muscle completely (Köllicker, 1856).

The Contracture Is Active.—The muscle is able to sustain a considerable weight throughout its contraction; the prolongation of the curve is therefore not due to a mere loss of elasticity, but is an active process. This is also shown by the facts that the formation of heat and the use of material are increased (Fick and Boehm). The energy efficiency is of the same order as in normal tetanus (Hartree and Hill, 1922), and the formation of lactic acid, and its prevention by iodoacetic acid, the splitting of phosphogen and the production of ammonia are as in ordinary muscular contraction (review, Bremer, 1932). The tension, the height and quickness of contraction, the irritability, the lifting and sustaining power of the muscle are all raised by veratrine (Dreser, 1890). It also lessens the effects of fatigue.

Influence of Conditions.—The effect of veratrine is enhanced by agencies which stimulate the muscle, such as moderate heat. The contracture is diminished by depression of the muscle produced by cold or excessive heat; by fatigue; or by muscular depressants, such as potassium, quinine or ether. Small doses of calcium increase the contracture, high doses remove it (Milheiro, 1926). Bacq, 1939, found that veratrine sensitizes striped and smooth muscle to the effects of K, Na, Rb, Cs, NH_4, and Ba, and believes that most of the effects of veratrine can be interpreted as sensitization to potassium. Dilutions of veratrine down to 1:10,000,000 cause frog's skeletal muscle to be contracted by dilutions of KCl which are ordinarily ineffective, so that veratrine may be used as a biological reagent for potassium ions. Aconitine and delphinine produce a similar sensitization.

Double-Peak Curve.—Veratrine curves generally show two imperfectly fused contractions (v. Bezold): a primary contraction, which occurs with the normal rapidity, but is somewhat higher than normal, and which tends to relax quickly; and a secondary contraction, which occurs more slowly and lasts longer. Overend, 1889, attributed this phenomenon to the different contraction velocity of the white and red muscle fibers, but Cervello and Weiss, 1899, showed that uniform muscles exhibit the same phenomenon. Riesser, 1921, found material differences in the response of the slow red and rapid white muscles of the rabbit, but this does not explain the double-peak phenomenon. Verzàr and Felter, 1914, attributed the action to increased sensitiveness to normal stimuli.

Veratrine acts directly on the muscle substance, for the effects occur after curare (Prevost, 1867), and in the nerve-free end of the sartorius muscle. Pretreatment with acetylcholine, physostigmine or neostigmine also does not alter the typical effects; nicotine enhances it (E. Frey and Weigmann, 1943). However, *veratrine produces analogous changes in the innervation.* If a portion of the motor nerve of a toad muscle is exposed to veratrine, a single shock applied to the nerve results in prolonged tetanic contraction, the after-discharge lasting from less than a second to a full minute (T. P. Feng, 1941). Querido, 1926, reported that the veratrine reaction diminishes with the *degeneration of the divided sciatic nerve,* until with complete nerve degeneration, direct stimulation of the muscle gives only a single twitch. In the *cat,* also, a single shock stimulation of a motor nerve after intra-arterial injection of veratrine, barium or guanidine causes prolonged repetitive discharges which are not affected by curare (Feng and Li, 1941; Acheson and Rosenblueth, 1941).

Other Substances Producing Veratrine Effects.—The prolonged contracture characteristic of veratrine, is by no means confined to this alkaloid, but is also produced by digitalin, helleborein, muscarine, strychnine, by aldehydes (Verzàr and Felter, 1915), and the like, by cold and by strong electric stimulation (Kruse, 1922). This *wide occurrence* signifies that the phenomenon is of fundamental physiologic importance. These measures also prolong the contraction of *cardiac and smooth muscles.*

The Action of Glycerin on Muscle.—The muscles of frogs poisoned with glycerin respond to single stimuli by prolonged contraction, the curve having a superficial resemblance to that of veratrine, but rather more irregular. The glycerin contraction, however, is a true tetanus, due to greater irritability of the muscle substance, the action current of each contraction sufficing to start another contraction. The phenomena occur also after curarization (Santesson, 1903).

Circulation.—The effects are complex. Those on excised hearts resemble those of aconite and digitalis (slowing with increased systole). In intact animals, stimulation of the vagus center predominates at first (marked slowing); later, the fall of pressure from vasomotor depression becomes prominent. Both actions are cardiovascular reflexes, probably arising from the ventricular region of the heart, with their afferent path in the vagus (Jarisch and Richter, 1939).

Mammalian Circulation.—Small doses sometimes cause primary quickening of the heart. With larger doses (0.025–0.05 mg. per Kg.) there is sudden and marked slowing with corresponding fall of blood pressure (Pilcher and Sollmann, 1915). The slowing is greatest soon after the injection, often with marked arrhythmia or temporary arrest. This acute effect is due to reflex stimulation of the vagus center; section of the vagi largely abolishes it, and stimulation of the vagus trunk does not produce further slowing (Busquet, 1907). With divided vagi, large doses may cause primary quickening and generally moderate rise of blood pressure. Cross circulation experiments also show that the veratridine slowing is partly due to reflexes from the heart, lungs and carotid sinus, partly to direct stimulation of the central nervous system (Krayer *et al.*, 1943). The fall of blood pressure is mainly due to the slowing, although some fall may occur independently (Lissauer). The vasomoter center is moderately stimulated by the respiratory embarrassment, even when the vagi are cut. The stimulation does not occur if artificial respiration is maintained (Pilcher and Sollmann, 1915).

Late Effects.—The acute effect soon passes off. The heart then beats with a steady, moderately slowed rate. This slowing is not removed by atropine and is therefore cardiac. The blood pressure falls progressively, occasionally interrupted by spasmodic rise from central vasomotor stimulation. The strength of the heart is not impaired, for it reacts well to compression of the aorta, and beats efficiently just before death. The fall must therefore be vasomotor; accordingly, sciatic stimulation or asphyxia fails to raise the pressure (Lissauer, 1887). The vagus remains excitable. The cerebral vessels are constricted (Dixon and Halliburton, 1910).

In *heart-lung preparations* (dogs), nontoxic doses of veratrine act chiefly on the cardiac muscle, increasing the total output and work (Krayer and Mendez, 1942).

The perfused mammalian heart (Hedbom-Langendorff) shows primary slowing from stimulation of the peripheral vagus mechanism; then irregularity and finally paralysis of the cardiac muscle. The tonus is increased.

Frog's Heart.—The effects resemble those of aconite and digitalis. They involve mainly the ventricle and consist in slowing (no further slowing on vagus stimulation; Busquet, 1907); prolonged systole and increased tonus; sudden change in the rate to one-half; "peristaltic" contractions; and final median standstill. High concentrations cause prompt systolic standstill, with continued shortening. The auricles continue much longer. The same effects occur on the excised and perfused heart (Boehm, 1913). The response to vagus stimulation is abolished (La Grutta, 1928). De Boer, 1917, attributed the slowing and halved rhythm to increase of the refractory period of the ventricle. If the rhythmic pulsations of the heart are suppressed by vagus stimulation, and the muscle is stimulated mechanically, veratrine prolongs the contracture, as in skeletal muscle (Querido, 1926).

Peripheral Action on Blood Vessels.—Veratrine produces powerful constriction, which may be removed by atropine or quinine. These antagonists do not prevent contracture by barium (Kondo, 1919).

Collapse Action.—The impairment of circulation, combined with emetic action, results in varying degrees of collapse, and thereby fall of temperature, analogous to veratrum.

The **respiration** is influenced by the circulatory and convulsive actions, and also directly. It is temporarily arrested during the acute fall of blood pressure, but may be depressed without any change of blood pressure. The respiratory embarrassment is generally diminished by atropine or division of the vagi (Pilcher and Sollmann, 1915). *Bronchial muscles* constrict in intact animals (Dixon and Brodie), but not in the excised trachea (Trendelenburg, 1912). Titone, 1913, observed that veratrine relaxed isolated bronchial muscles.

Convulsions.—These are commonly present in mammals and frogs, and are probably medullary. Rabbits and guinea pigs show convulsive "bucking." *Cerebral functions* are scarcely affected.

Ureter.—Cevadine increases the tonus and contractions of excised ureter (Rossi, 1919).

Tissue Oxidation.—Cevadine inhibits the oxygen uptake of mammalian tissue, but accelerates it in yeast (Bernheim and Bernheim, 1933).

Local Action.—Cevadine is strongly irritant, resembling aconite. Applied to the skin, it produces burning, later a cold sensation and partial anesthesia, with reddening and sometimes discrete vesication. The irritation is especially strong on the abraded skin, 1:100,000 solution producing tingling and "shooting" pain (Sollmann and Pilcher, 1916). On mucous membranes it causes acute catarrh—sneezing, coryza, gastro-enteritis, vomiting, diarrhea, and so forth; sometimes with corrosive lesions. The *vomiting*, however, is mainly central (Eggleston and Hatcher, 1915). In frogs, the secretion of *mucus* from the skin is greatly increased.

Therapeutic Uses.—Veratrine is used locally as counterirritant, in neuralgias and similar conditions, as 2 to 4 per cent ointment. Sabadilla seeds are employed against pediculosis capitis (salve, 1:4; decoction, 5:200). The irritation is severe, and absorption has caused serious symptoms. The internal use of veratrine (against fever), even in milligram doses, has produced gastro-enteritis.

Absorption is rapid; little is known about the *excretion*, but it probably occurs by the kidneys.

Symptoms of poisoning in man resemble those of aconite poisoning: burning in mouth, spreading to stomach; increased salivation, vomiting, diarrhea, abdominal pain; anxiety, headache, giddiness; pupils dilated; pulse slow and feeble, later irregular; weakness, twitchings in muscles. Death by respiratory and circulatory collapse. Consciousness preserved till the end. Post mortem, often intestinal ecchymoses. In *nonfatal doses*, the symptoms are slow in disappearing, and *slow poisoning* by continued small doses is on record: two patients became weak and thin, suffered from bloody diarrhea, insomnia, disturbance of the intellect, and delirium. The *treatment* is the same as in aconite poisoning. As the veratrine is believed to be rapidly excreted through the urine, it is well to administer hot tea as a diuretic.

Assay.—The gastrocnemius of frog, or leech muscle, may be used, with observations of details to differentiate it from aconitine, colchicine and quinine (Hummelsheim, 1933).

Veratrine is a mixture of alkaloids obtained from the seeds of Asagraea officinalis. Very slightly sol. in water (1:1760); freely sol. in alc. (1:2.8). Its internal use is not advisable, but it has been given in doses of 2 mg. Externally, it is applied as ointments of 2 to 4 per cent. *Maximum dose*, 5 mg.

Zygadenus (Death Camas), Liliaceae, a poisonous plant of western stock ranges, owes its toxicity to veratrine bases. It contains at least sabadine, sabadinine and veratralbine (Slade, 1905). The actions of the Zygadenus alkaloids were studied by Mitchell and Smith, 1911. The literature is given by Marsh and Clawson, 1915.

Andromedotoxin is a N-free neutral principle, isolated by Plugge from *rhododendron* and similar plants. It seems to belong to this group. Species of rhododendron have been used as medicine by the Chinese. Their actions have been investigated by H. P. Chu and How, 1931.

Kalmia, Mountain Laurel and Sheep Laurel are important as stock poisons (Crawford, 1908). Kalmia angustifolia was studied by Waud, 1940. It prolongs the contraction of skeletal muscle, slows the frog heart (not prevented by atropine), constricts bronchial muscle (relaxed by epinephrine, not by nitrite), stimulates the movements of small intestine (not antagonized by epinephrine), and has no effect on the uterus.

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VERATRUM

Vera'trum Viride and Album (Green and White Hellebore) seem to be mere varieties (the green American, the white European), with practically identical actions and composition. They owe their activity mainly to the alkaloid *protoveratrine*. A number of other related but less active alkaloids are present (Cramer, 1915). The effects of protoveratrine, and therefore of veratrum, are qualitatively similar to those of cevadine, but the characteristic muscular and irritant actions of cevadine are insignificant in protoveratrine. The most important effects of veratrum are on the medulla, and especially on the circulation, resulting in vagus stimulation, slowed pulse, fall of blood pressure, sweating, "collapse action," and reduction of temperature. It has been employed as a "cardiac depressant," especially in eclampsia, but it is obsolete. Protoveratrine is more toxic than cevadine, approaching aconitine; but the prompt evacuation of overdoses by emesis (central) renders veratrum relatively safe.

Constituents.—The most important alkaloid of Veratrum album, although not the most abundant (0.03 to 0.08 per cent), is *Protoveratrine* (Salzberger, 1890). The other alkaloids are: *Jervine*, 0.1 per cent, weakly active; traces of *Rubijervine* (almost inactive); the inactive *pseudojervine* or protoveratridine, which is probably a decomposition product; the glucoside veratramine; and veratroidine and veratrabline, which are probably mixtures of amorphous bases. Traces of cevadine have been reported in V. viride, but are doubtful.

Black Hellebore, Helleborus niger, is in no way related to veratrum. Its active principle, helleborein, belongs to the digitalis group.

Experimental Effects on Respiration and Circulation.—The typical effects of intravenous injection of Veratrum Viride consist in brief but marked depression of the respiration, slowing of the pulse, and lowering of blood pressure. These effects are largely prevented by section of the vagi, and do not recur if further doses of the Veratrum are injected. Repeated injections generally produce marked rise of blood pressure, especially if the vagi are intact. The effects are probably due to protoveratrine (H. C. Wood, Jr., 1906; Cramer, 1915; Pilcher and Sollmann, 1915).

Sensory Actions.—Dried Veratrum or protoveratrine is irritant, provoking sneezing, and other effects, but in solutions the irritant effects are slight. These have a marked anesthetic action, lasting forty-eight hours, on the cornea (Eden).

General Symptoms in Mammals.—The first effects are nauseant and emetic, often so severe as to obscure other symptoms. Of these, the respiratory changes are characteristic, especially in rabbits. They consist in periodic dyspneic attacks, culminating in convulsions of a medullary type. The respiratory disturbance is probably due to the combined influence on the respiratory and other medullary centers, circulatory changes and muscular exhaustion. In the intervals the respiration is regular. *Death* occurs late, with the circulation fairly preserved and consciousness present to the end (Eden).

Collapse Action.—The combination of the central, circulatory and muscular depression, nausea and dyspnea, results more or less in collapse. This and the profuse sweating lower the *temperature*, proportional to the general symptoms (Eden).

Effects of Therapeutic Doses on Man.—Full doses constantly produce a slowing of the pulse to about 62 per minute (irrespective of the original rate), and generally a fall of systolic and diastolic blood pressure of about 35 mm. The slowing and fall are proportional to the dose. Electrocardiograms show no effect (Collins and Hanzlik, 1918). The blood flow in the arm is markedly lowered by therapeutic doses (Hewlett, 1917). Respiration is not disturbed. Headache, gastric burning, nausea and vomiting may set in, but come after the depression of the circulation, and are therefore not its cause. The effects last for several hours. Large doses (4 cc. of 10 per cent tincturewithin half an hour) may produce more serious and lasting collapse, with a pulse rate of 40 or 30, suddenly returning to normal after eight or nine hours.

Veratrum Poisoning.—Although protoveratrine is highly toxic, veratrum is vomited so promptly that death is rare even with large doses (Wood). It has, however, been reported after 1 to 2 Gm. of the powdered White Hellebore (which is used as insect powder), and in enfeebled patients from a teaspoon of the Tincture. The *symptoms* are burning, vomiting and diarrhea, dysphagia, collapse, paralysis or light convulsions. For treatment, the stomach should be emptied by warm water or lavage, and the collapse treated along the usual lines.

Therapeutic Uses.—Veratrum is probably the most active and reliable *cardiac depressant,* and was formerly much used to slow and soften the pulse and lower the blood pressure, especially in eclampsia and other conditions of high blood pressure. F. E. Whitacre *et al.*, 1947, claim that it relaxes the angiospasm which appears to be a chief factor in eclampsia. Pesci, 1906, claimed that it lowers the blood pressure by 7 to 50 mm., slows the pulse, increases diuresis and lessens uremia. Haultain, 1914, made similar claims, but J. R. Willson, 1944, reports that the fall of blood pressure markedly diminishes the urine output and depresses urea clearance in hypertensive toxemias of pregnancy. H. Goldblatt *et al.*, 1942, found it of no value in experimental renal ischemia. It was used for the same purposes, and to lower the temperature, in the early stages of sthenic fevers (pneumonia) and other acute infections. The effects are probably mainly due to the cardiac slowing from vagus stimulation and to the nausea. Veratrum with other cardiac depressants has gone out of fashion. It is contraindicated in asthenic conditions (cardiac weakness, general debility, typhoid, and so forth.

Response in Pathologic Conditions.—Collins, 1916, observed the most marked effects in cases of hypertonus, the systolic pressure falling more than the diastolic. Little or no response was obtained in arteriosclerosis, paroxysmal tachycardia or heart block.

Administration.—Veratrum is given in repeated doses—1 cc., 15 minims, of the Tincture (N.F.) every half hour or hour, till the skin becomes moist, the pulse slower and slight nausea is present. It may then be stopped. The desirable range is 3 to 4 cc. (Collins and Hanzlik, 1918). Caution is necessary if a total of 4 cc. is exceeded. If vomiting should appear before the other effects, 5 to 10 drops of Tr. Opii are administered with each dose of Veratrum. Repetition of the dosage does not inhibit the action (as occurs with intravenous injections in animals).

Bio-Assay.—Commercial preparations vary considerably in activity. As the drug contains a number of active principles, its efficiency cannot be estimated by alkaloidal assay. The determination of the minimum fatal dose for frogs or guinea pigs is a convenient method. It averages about 2.3 mg. of drug per Gm. of frog, and 0.24 mg. per Gm. of guinea pig (Pilcher, 1917). Rowe, 1925, proposed mice, as more rapid and accurate. The M.F.D. is ¼ mg. per Gm., intraperitoneally.

PROTOVERATRINE

The *actions* of protoveratrine and its derived alkaloids have been reinvestigated by Krayer *et al.*, 1944. The effects of protoveratrine, as described by Eden, 1892, are similar to those of veratrum. In mammals, moderate doses by vein produce temporary fall of pressure, absent if the vagi have been cut. This action is short, the pressure rising rather suddenly 40 to 50 mm. above normal, with increase of pulse rate, and inexcitability of the vagus. The rise is probably due to vagus paralysis. This is also of short duration. With repeated injections, the vagus paralysis becomes permanent, and the primary fall of pressure is absent, there being instead a small rise. *Toxic doses* produce cardiac arrhythmia, with periods of stoppage and corresponding changes of blood pressure. The rate in the intervals is at first rapid, then falls with the blood pressure. The vasomotor center becomes paralyzed.

Frog's Heart.—The effects are mainly depressant: the systoles are somewhat prolonged, but the tone is scarcely increased. Soon the ventricular rate is reduced to half, as with cevadine, aconite or digitalis; but this is interrupted by short periods of total arrest of the ventricle or auricles, apparently due to exhaustion of the muscle. Finally the heart stops in diastole, with relatively small doses (Boehm, 1913).

Motor System.—In frogs poisoned by protoveratrine, the reflexes disappear early. This paralysis is largely *central,* for it occurs also if the poison is excluded from the muscles by ligature. However, there are also *peripheral effects:* the muscles may respond normally to a single stimulus or contract even somewhat more quickly and efficiently; but they fatigue rapidly (Eden, 1892). The prolonged contraction characteristic of cevadine is indicated faintly, if at all, under ordinary conditions; but it may be elicited in excised muscles if precautions are taken against fatigue (Boehm, 1913). The nerve trunks are paralyzed only by concentrated solutions; the negative variation is said to be prolonged.

Jervine.—The effects also resemble those of veratrum, but the quantity of this alkaloid in the drug is too small to have any noticeable effect on circulation (Wood, Jr., 1906). With effective doses, the heart rate is first slowed, then rapid. The blood pressure falls progressively, presumably by depression of the cardiac muscle and vasomotor center. The respiration fails simultaneously (Wood, 1874).

Rubijervine.—Wood, 1874, found that "veratroidine," which was probably an impure rubijervine, acted mainly on the respiratory center, with some cardiac depression. Its quantity is also too small to be important.

Veratrum Viride, N.F. (Green or American Hellebore), is the dried rhizome and roots of Veratrum Viride. The dose of the 10 per cent *Tincture* is 1 cc., 15 minims. Till 1900 the Tincture was 40 per cent. Norwood's Tincture was supposed to be a saturated solution of the fresh root. *Veratrum Album* (White Hellebore) is probably a mere variety of the former, growing in Europe. It is used in the same doses.

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APOMORPHINE

Apomorphine is an artificial alkaloid, formed by dehydrating morphine through concentrated mineral acids. The removal of the molecule of water is the result of vigorous reactions that profoundly affect the structure (Pschorr). The actions of the base that is formed differ radically from those of morphine. It does not cause narcosis; its chief effect is emesis, by direct stimulation of the vomiting center, with prolonged and severe nausea which may result in collapse. Small doses are sedative and hypnotic; larger doses cause excitement, convulsions and death by asphyxia. It produces direct depression of excised cardiac and skeletal muscle. Apomorphine is the preeminent centrally acting emetic, especially useful for hypodermic administration in poisoning. The prolonged nausea is disagreeable, and the depression may be dangerous.

Absorption.—Apomorphine is readily absorbed from all mucous membranes. Emesis is produced by applying a few milligrams to the conjunctiva of a dog; also from application to the urethra, vagina, and the like (Macht, 1917).

Fate.—The greater part appears to be destroyed. None is converted into morphine (Bamford, 1930).

The Emetic Action of Apomorphine Is Central.—The specific emetic action of apomorphine was announced by Gee, 1869, the year of the discovery of the substance by Matthieson and Wright. The emesis is promptly produced by small doses, with little preliminary nausea. The fact that there is no evidence of gastric irritation (Gee, 1869), and that apomorphine is more effective hypodermically than by mouth (Siebert, 1871), indicates that its emetic action is not a reflex from irritation of the pharyngeal or gastric mucosa, as is the action of most emetics; but that the apomorphine emesis must result from a central action, a direct stimulation of the hypothetical vomiting center in the medulla. The crucial proof was brought by Eggleston and Hatcher, 1912, who found that the typical phenomena associated with vomiting can be produced by the injection of apomorphine into animals whose entire alimentary canal had been removed, from the cardia to the anus. These eviscerated animals show the retching, the vomiting movements and the expulsion of mucus from the mouth and esophagus. Direct application of the apomorphine to the esophagus or pharynx does not produce vomiting. Emesis occurs if a small quantity of apomorphine (0.0001 mg. per Kg.) is applied directly to the floor of the fourth ventricle, in the region of the vomiting center (Thumas, 1891). Most other emetics also produce vomiting when applied to this region, and so do strychnine, histamine, choline and epinephrine (Weiss and Hatcher, 1923). This response does not occur if the sensory nuclei of the vagus have been destroyed. Hatcher and Weiss, 1923, believe that apomorphine and presumably the other emetics merely lower the threshold of the center to reflexes ordinarily not emetic.

Siebert, 1871, gave emetic doses of apomorphine to dogs daily for six weeks, and found *no signs of inflammation* at autopsy. Eggleston and Hatcher found that dogs require by vein only 1/25 of the oral dose, and vomiting occurs in one-half the time. Only traces of apomorphine are excreted into the stomach, even after enormous hypodermic doses (Bamford, 1930). With locally acting emetics vomiting does not occur *if both vagi are divided* (Openchowski, 1889), but this does not prevent apomorphine emesis (Siebert, Harnak and others). Magendie found apomorphine effective after replacing the stomach by a pig's bladder.

Antiemetic Drugs.—Apomorphine vomiting is not affected by local sedatives (bismuth and the like). but is prevented by narcotics. With chloroform and chloral, full narcotic doses are needed; but with morphine and its esters, small, non-narcotic doses suffice. Papaverine is ineffective (Ruth, 1913); also atropine. Calcium chloride. intravenously, inhibits the emesis for several hours, and also antagonizes apomorphine in some other directions (di Mattei, 1927).

The *movements of the stomach in emesis* were investigated in cats by the x-ray method (Cannon, 1898). The same events follow apomorphine and mustard; the first effect is total inhibition of the tone of the cardial portion, which becomes a flaccid bag. The pyloric end is shut off by a deep contraction ring. The contents are then expelled by sudden contraction of the diaphragm and abdominal muscles. As the expulsions are repeated, the gastric walls tighten around the remaining contents. Kratinoff and Sack, 1927, who observed the gastric movements under apomorphine in dogs with fistulae, and in decerebrate cats, reported that active gastric and intestinal movements precede the contractions of the abdominal muscles and diaphragm.

Susceptibility of Different Animals to Emetic Action.—Animals incapable of vomiting (rabbit, rat, guinea pig. horse, cattle, and so on) do not do so under apomorphine; but many animals which vomit more or less readily in response to local irritants are also completely insusceptible (pigs, birds, frog) or relatively insusceptible to apomorphine emesis (the cat requires about fifty times more per body weight, hypodermically, than the dog). Man and dog are the most susceptible. Continued administration does not establish tolerance (Siebert). Insusceptibility to the emetic actions does not imply tolerance of the other central actions of apomorphine, to which all animals are susceptible.

Recalcitrant Stage.—Excessive doses of apomorphine are not so effective as moderate doses in producing emesis, and may render the animal completely recalcitrant to the emetic action (Eggleston and Hatcher).

Clinical Dosage.—For emetic effect, 5 mg. (1/12 grain) or at most 10 mg. (1/6 grain) of the crystallized hydrochloride, in ½ to 1 cc. of water, should be given hypodermically, and repeated in fifteen minutes if necessary. As a nauseant expectorant, it is inferior to ipecac, but may be used by mouth, in syrup of citric acid, in doses of 2 to 10 mg. (1/30 to 1/6 grain) for adults; ½ to 2 mg. (1/120 to 1/30 grain) for children. This dosage does not cause depression. L. J. Needler, 1944, reports that 3 to 6 mg. injected hypodermically promptly arrest attacks of *paroxysmal tachycardia*, restoring the normal ryhthm during the nausea, with relaxation after emesis.

Onset and Duration of the Emetic Action.—In man, the hypodermic injection of 5 to 10 mg. (1/12 to 1/6 grain) of apomorphine produces severe nausea and vomiting within ten or fifteen minutes. By mouth, twice this dose is uncertain. The emesis may be repeated several times. The nausea is intense and is likely to persist longer than with the reflex emetics, since the apomorphine is not removed.

The **phenomena of nausea** are common to all emetics. They consist in a feeling of sickness, lassitude and weakness; pale skin; increased secretion of sweat, saliva, mucus and tears; sensation of excessive heat; increase of respiration and pulse rate; fall of blood pressure. *During the emesis proper*, the contraction of the abdomen raises the blood pressure spasmodically. This contraindicates emesis in apoplectic patients and the like.

Circulation and Respiration in Nausea and Vomiting.—Traube, 1867, described initial fall of pressure, with slow vagus pulse, succeeded by quickened pulse toward the end of the emetic action. Brooks and Luckhardt, 1915, and Miller, 1915, found emesis accompanied by marked disturbances of the circulation and respiration. There is sometimes a period of elevated pressure; but at the moment of emesis, the heart is usually inhibited, with sudden severe fall of blood pressure. This is interrupted by periods of great oscillations. These great and sudden changes may rupture blood vessels, which would resist more gradual changes of equal degree. *The changes are somewhat different in the two types of vomiting.* (1) Rapid projectile type, with short nausea: during the nausea, the blood pressure is slightly raised, the pulse rate increased, its amplitude diminished. During the vomiting, the pressure falls sharply with practically complete arrest of the heart, or arrhythmia. The respiration is suspended. After the expulsion, rapid recovery occurs to normal. (2) Slow, labored type, with more marked nausea, and so forth: during the nausea, there is deep breathing and salivation. During violent retching, the blood pressure and the intrathoracic pressure oscillate greatly. The pulse is slow and irregular. During the vomiting, the changes are as described. The slowing and fall of blood pressure are due to inhibiting vagus stimulation, since they are prevented by atropine. The oscillations are indirect results of the muscular efforts, and are generally eliminated by curare (Harnack, 1874). *The stimulation of the salivary centers* was studied by V. E. Henderson, 1910.

Accidents in the Therapeutic Use of Apomorphine.—Apomorphine nausea may produce considerable depression, varying in degree in different individuals. It is characterized by muscular debility, and rarely collapse (Harnack, 1908). These may precede or follow the emesis, and are especially liable to occur in the rare cases in which the emesis fails: in pulmonary and cardiac disease; in debilitated patients and in children. The collapse is preceded by irregular respiration, anxiety, vertigo and fainting. During the collapse, the patient may be unconscious and pass into early death. These cases are exceptional, but their possibility should be borne in mind. It is believed by some that the accidents are often due to impurities, so that only freshly made solutions of the crystallized alkaloid should be used, never of the amorphous.

Other Central Actions.—If apomorphine is given in larger doses it produces a series of *excitant effects*, especially in animals which do not vomit (Harnack, 1874). At first there is great restlessness, gnawing, excitement and terror. The gnawing is not seen with rabbits from which the hemispheres have been removed, so that it must be of cerebral origin (Morita, 1915). The respiration is quickened (even under chloral narcosis), but regular. Apomorphine disturbs *heat regulation*, so that animals do not respond to fever by polypnea and shivering (Magne, 1914). With doses larger than are used in man there are ataxia and then violent irregular *convulsions*. These interfere with respiration, and the animal dies in asphyxia. Death occurs also if the convulsions are suppressed by chloral, but then requires a dosage twenty times as high. Frogs exhibit the same phenomena. Hattori, 1910, found that the reflexes from the spinal cord and brain are increased. Apomorphine produces *hyperglycemia* in well fed rabbits (Campbell and Morgan, 1933). The effects on the *intestinal* movements and tonus are variable, in unanesthetized dogs with Thiry-Vella intestinal loops (Gruber, Haury and Drake, 1939).

Hypnotic Action of Apomorphine and Use in Acute Alcoholism and Hysteria.—Small, nonemetic doses (2 mg.) act as a safe and certain hypnotic, effective even in delirium; natural and refreshing sleep occurs usually in five to twenty-five minutes (J. C. Douglas, 1899; Coleman and Polk; 1902). Other observers (Rosebrugh, 1908) report similar results; the tendency, however, has been to use doses (5 mg.) which produce an emetic action. This perhaps aids the therapeutic effect by breaking into the fixed ideas of such patients. The sleep occurs in a few minutes after emesis. Hypodermic administration secures by far the best results.

Local Application.—Harnak, 1874, showed that this paralyzes *cardiac and skeletal muscles* in frogs. The depressant action on the rhythmicity of the heart was studied by Navratil, 1928.

***Apomorphine Hydrochloride, U.S.P.**, is prepared from morphine by the abstraction of one molecule of water. The official is a definite chemical substance with four benzene rings. The preparations of different manufacturers differ more or less in composition and activity (Harnak, 1909). Minute, white or grayish-white, glistening prisms; odorless; acquiring a greenish tint upon exposure to light and air. Must be rejected if it at once imparts an emerald-green color to 100 parts of distilled water. Sol. in water (1:50) and in alc. (1:50). Dose, expectorant, 1 to 2 mg., 1/64 to 1/32 grain; emetic, by hypodermic injection, 2 to 8 mg., 1/32 to 1/8 grain; maximum, 20 mg., 1/3 grain. *Apomorphine Hydrochloride Tablets*, U.S.P.; usual size, 5 mg.

Old solutions of apomorphine acquire a deep green color, indicating decomposition. The emetic action may not be affected by this change in some samples, but it is lost in others (Harnack, 1874).

Chloromorphids are formed in the manufacture of apomorphine if the action of the hydrochloric acid on the morphine is not carried sufficiently far. They are, therefore, a frequent contamination of commercial apomorphine. They are chemically analogous to acetylmorphine, being formed by the substitution of Cl for the OH group of morphine. Their pharmacologic actions are similar to those of acetyl-morphine (heroin), namely, exaggerated morphine effects, with greatly increased toxicity, paralysis of respiration, and an antiemetic action (Harnak and Hildebrandt, 1911). These investigators hold these impurities responsible for the failure of emesis and the collapse.

Apocodeine is derived from codeine. It is not a definite compound (as is apomorphine), but consists of mixtures, varying in composition according to the methods of manufacture (Small and Lutz, 1932). Different samples vary in potency, but their actions are similar (Krayer, 1926). Dixon, 1903, reported that it paralyzes successively the nerve endings of the vagus, vasomotors, other smooth muscle, striped muscle and cardiac accelerator, as well as the nerve centers, but its action does not seem to be absolutely specific. Magnus, 1905, found both stimulant and paralyzant peripheral effects on peristalsis. It has been used as expectorant, emetic, hypnotic and cathartic (Fraenkel).

ASPIDOSPERMA (QUEBRACHO)

The bark of Aspidosperma Quebracho-blanco contains several alkaloids with similar actions: fall of blood pressure, increased heart rate, clonic convulsions with muscular weakness, and a great and persistent increase of the rate and depth of respiration. The lungs are markedly hyperemic (Harnack and Hoffmann, 1884; Wood, 1910). These actions are partly central, partly peripheral. Wood, 1908, attributed the respiratory effect to intense irritation of local areas of the lung, which is observable at autopsy. The alkaloid quebrachine is mainly responsible for this effect. One of the alkaloids, aspidosamine, produces emesis; the others only nausea, with its usual accompaniments. Cow, 1914, found that larger doses paralyze the nerve cells of the autonomic system, brain and spinal cord. Still larger doses paralyze the vagus, sympathetic and motor endings, similarly to nicotine and curare. Death occurs by paralysis of the respiratory center when the motor nerves still respond to stimulation.

Hesse claimed to have isolated six alkaloids; but of these only two are well characterized, namely, aspidospermine and quebrachine, the latter *identical with yohimbine*. The others were probably impure mixtures and cleavage products (Ewins, 1914).

Aspidosperma has been used as a respiratory stimulant in dyspnea and asthma, but its usefulness is doubtful. Its irritant action on the lungs and the circulatory depression should be borne in mind. The dose of the fluidextract is 1 to 4 cc.; of the amorphous aspidospermine (a crude mixture), 0.06 to 0.1 Gm.; of the crystalline (true aspidospermine chloride), 5 to 30 mg., at first every hour or two, then less frequently (S. Solis-Cohen).

IPECACUANHA AND EMETINE

Ipecac, the root of a Brazilian plant, contains several alkaloids, of which two, emetine and cephaeline, produce local irritation and nausea and emesis, by central and local action. Large doses have specific effects against *amebic dysentery*. These will be discussed with other amebicides (see Index). The systemic actions (central and cardiac depression; stimulation and depression of smooth muscle) do not occur when the drug is administered by mouth, since little is absorbed.

The **nauseant and emetic actions** are produced much more slowly than with apomorphine. In man, vomiting occurs only after one-half to one hour. The drug is therefore more useful as a nauseant expectorant than as an emetic. *As expectorant*, the Syrup is employed (1 cc.). An infusion, used as a gargle, has been recommended to avoid irritation of the stomach. *For emesis*, the powdered ipecac may be administered, 0.5 to 2 Gm. in warm water, repeated in half an hour if necessary; or the Syrup (tablespoon for adults, teaspoon for infants, especially in spasmodic croup). It has some advantage over the mineral emetics in that it causes less gastric irritation and less general depression; but its use is practically restricted to the relief of spasmodic croup in pediatric practice, giving a teaspoonful of Syrup of Ipecac every ten to fifteen minutes till emesis occurs.

The location of the emetic action is chiefly central, for vomiting movements occur in eviscerated animals, and it is practically as effective by intravenous as by oral administration (Eggleston and Hatcher, 1915). The response on gastric injection is more prompt, suggesting that the local action facilitates the emetic response. Emetine and cephaeline act alike, except that cephaeline is twice as potent.

Emetine is partly *excreted* into the stomach (Valenti, 1911) and intestine (d'Ornella, 1873).

Irritant Action.—Ipecac irritates all mucous surfaces and may produce conjunctivitis, bronchitis, skin eruptions, asthma, diarrhea, rectal irritation, and so on. Some persons are extremely sensitive to these effects. On the abraded skin, 1 per cent solution of emetine raises a wheal (Sollmann and Pilcher, 1916). Hypersensitive patients also react with urticaria to systemic administration (Savignac and Alivasatos, 1919), or with eczema or asthma. Widal *et al.*, 1922, claimed that these can be desensitized. The *subcutaneous tissue* is but little subject to irritation by ipecac (Zepf, 1903), perhaps because the drug is too rapidly absorbed. Renal irritation occurs rarely.

Use in Dyspepsias.—The gastric hyperemia, produced by small doses, has been used in dyspepsias (a drop or two of the syrup in a teaspoon of water, every fifteen minutes). The benefits are doubtful.

Emetine in Pyorrhea Alveolaris.—The supposed causation of Rigg's disease by endamebae prompted the trial of emetine. Many observers reported good results, but neither these nor the etiology are beyond dispute (Price and Bensing, 1915). Smith and Barrett, and others, found Endamoeba gingivalis constantly present in the lesions, and introduced the local use of ipecac. Bass and Jones, 1915, were especially enthusiastic. They reported the amebae destroyed by hypodermic injections of emetine, 0.03 Gm. daily for three to six days.

Use in Other Parasitic Conditions.—Emetine is the drug of choice against certain *flukes* (Fasciola and Paragonium), 1 mg. per Kg. (to a maximum of 65 mg.), intramuscularly, once daily for a maximum of five days. It has been unsuccessful in syphilis, rabies, trypanosomiasis and bacillary dysentery. Marked improvement was reported for sprue by Schmitter, 1915.

Malignant Tumors.—It was reported that these may disappear after local injection of emetine. However, this is due merely to the caustic action (Lewisohn, 1918).

Systemic effects occur only after hypodermic or intravenous doses. They consist in acute fall of blood pressure, chiefly from cardiac depression, with ventricular fibrillation by large doses (emetine produces diastolic arrest of the isolated frog heart; Moulinier, 1914). Nontoxic intravenous injections lower the carotid pressure, but increase the pressure in the pulmonary artery and vein, and also the pulse rate. Larger doses dilate the pulmonary vessels, but generally less than the systemic vessels. The heart is also depressed. Hypodermic injection does not affect the circulation acutely (Plumier and Clermont, 1919). Most patients under emetine therapy show inversion of the T wave without clinical evidence of myocardial insufficiency (Cottrell and Hayward, 1945).

If the action of toxic doses has lasted any time, the autopsy shows marked *gastro-enteritis* with ecchymoses and even ulcers. There are also hemorrhages into the lymph glands, spleen and kidneys (Kilgore and Liu, 1917). Even fatal doses produce only slight degeneration of renal parenchyma (De la Paz and Montenegro, 1918).

Emetine has been tried in *tuberculous hemoptysis*, the reports being often favorable, but not very critical. The mechanism is not explained. Flandin, 1913, claimed immediate arrest after the hypodermic injection of 40 mg., without unpleasant symptoms. The injection may be repeated in intervals of twelve to twenty-four hours. Nicola, 1914, employing the same dosage as Flandin in hemoptysis, obtained variable results.

Smooth Muscle.—Pick and Wasicky, 1916, pointed out that emetine is related to papaverine in action as well as in chemical constitution. It paralyzes the smooth muscle of the digestive tract, bronchi, uterus and vessels (but small doses stimulate peristalsis). The depressant action is exerted directly on the muscle substance, emetine being mutually antagonistic with barium.

Uric acid excretion is increased by ipecac, as by other gastro-intestinal irritants (Abl, 1913).

Comparative Action of Emetine and Cephaeline.—Emetine is methylcephaeline (Carr and Pyman, 1913). Their actions agree qualitatively; but emetine is the stronger amebicide, while cephaeline is more irritant, more emetic (about twice, Eggleston and Hatcher, 1915) and about twice as toxic (Paul and Cowney, 1901). Emetine was said to be more depressing to the heart, and cephaeline is somewhat hemolytic.

Walters and Koch, 1917, tested *other cephaeline esters*. They found only quantitative differences. *Psychotrine*, the third alkaloid of ipecac, is also chemically related to cephaeline. It has a low toxicity (Walters and Koch). The amount in the drug is small and unimportant. Lloyd announced a colloidal alkaloid ("kryptonine") in ipecac. *Ipecacuanhin* is a crystalline glucosidal constituent (Finnemore and Braithwaite, 1912).

Ipecacuanhic Acid.—A further constituent, ipecacuanhic acid, was, until recently, considered a bearer of the action of ipecac in dysentery, but is inactive. It has the characters of caffeotannic acid (see Index), from which it differs only by one atom of oxygen. They differ from ordinary tannic acid, and are neither antiseptic nor astringent (Kimura, 1903).

PREPARATIONS.—*Ipecac*, U.S.P., is the dried rhizome and roots of Cephaëlis Ipecacuanha or acuminata, containing at least 2 per cent of alkaloids. Walters and Koch, 1917, found that both varieties contain about twice as much emetine as cephaeline. The drug was introduced into Europe about the end of the seventeenth century. It may be administered as the *Fluidextract*, U.S.P.; dose, as expectorant, 0.06 cc., 1 minim, or as emetic, 0.5 cc., 8 minims; or as the *Ipecac Syrup*, U.S.P., 7 per cent of Fluidextract; dose, as expectorant, 0.75 cc., 12 minims; as emetic, 8 cc., 2 drachms. ***Emetine Hydrochloride**, U.S.P., obtained from ipecac or by methylation of cephaeline; it is freely soluble in water or alcohol. Dose, daily, by parenteral injection, 30 to 60 mg., ½ to 1 grain. *Emetine Hydrochloride Injection*, U.S.P., in aqueous solution adjusted to *p*H 3.5; usual sizes of ampuls, 20, 30 and 60 mg. in 1 cc. Care must be used to keep it from contact with the eyes, as it is highly irritant. *Cephaeline* is administered in pills or as powder with sugar in a dose of 5 to 10 mg., 1/12 to 1/6 grain.

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THERAPEUTIC USE OF NAUSEANT EXPECTORANTS

Small doses of emetics increase bronchial and salivary secretion and sweat, which is useful in the early, congestive ("dry") stage of colds and in "dry" coughs. The dose should be sufficiently small to minimize general depression and noticeable gastric disturbance, although sometimes this cannot be avoided. The nauseants should be given every two to four hours. For the "abortion" of colds, ipecac is often employed in the form of "Dover's Powder," 0.5 Gm. at night. In the congestive stage, the syrup of ipecac may be used. *Tartar Emetic* may be substituted, but is more depressant, and its continued use may give rise to poisoning. Its expectorant dose is 5 mg. (1/12 grain). Viscid, adherent mucus may be thinned by *Ammonium Chloride* or *Carbonate* (0.2 Gm.), or *Potassium Iodide* (0.2 Gm.), or by the irritant saponin of *Syrup of Senega* (2 cc.).

The **reactions of the salivary center** were studied by V. E. Henderson, 1910. He found that it is readily depressed by *anesthetics* and by *morphine*, even in small doses. *Iodides* and other salts do not cause direct stimulation, but may act reflexly. *Emetine* stimulates both directly and reflexly, as do also *ammonium salts*, but with these the reflex stimulation is the more important. *Antimony* acts only reflexly, *apomorphine* only centrally.

Bronchial Secretion.—J. L. Miller, 1914, could not demonstrate any effect with therapeutic doses of emetine, ammonium chloride or carbonate. Large doses produced an increase, even when administered by duodenum.

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LOCALLY ACTING EMETICS

Numerous afferent paths may reflexly stimulate the vomiting centers, but for practical therapeutic purposes only those of the pharynx and gastric mucosa are available. Not every form of gastric irritation results in vomiting—the kind, rather than the degree, of irritation being important. This, and the necessity of avoiding severe local and systemic effects, limits the number of irritants which may be used as therapeutic emetics. However, there is still a wide choice, adapted to the various indications.

Cupric Sulfate and *Zinc Sulfate* act practically alike, provoking the vomiting reflex before there is time for other local irritant action. They are not absorbed (unless the stomach is corroded), and therefore do not lead to systemic effects. Vomiting occurs with certainty in a few minutes. The nausea is therefore short, and the after-depression is small, constituting an advantage over apomorphine. They are especially useful to empty the stomach of indigestible food or poisons (provided that these are not corrosive). Copper sulfate is of especial value in *phosphorus poisoning* if any of the poison is still in the stomach, since the metallic copper is precipitated and forms an impermeable coating over the unabsorbed phosphorus particles. The emetic dose of copper sulfate is 0.25 Gm. in 1 per cent solution; that of zinc sulfate is 1 to 2 Gm. They may be repeated in fifteen minutes if necessary. A teaspoonful of *powdered mustard* in a cup of warm (not hot) water, repeated every fifteen minutes, is a rather uncertain emetic, but a useful emergency remedy in poisoning, when the patient is already disposed to vomit. *Salt water*, or even plain warm water, or tickling of the fauces, may be similarly useful.

Antimony and potassium tartrate (tartar emetic) acts similarly to copper, mainly by a local effect, but its use should be avoided, since it is very depressing. It is fairly easily absorbed, so that 0.2 Gm. has repeatedly proved fatal. The ordinary emetic dose is 30 mg.; and if this is not effective in half an hour, it would be well to give tannin as an antidote. *Emesis as an undesirable side action* occurs with digitalis, squill, apocynum, salicylates, senega and a large number of other drugs. The action may be local or central, often both.

The **site of action of miscellaneous emetics** was investigated by Eggleston and Hatcher, 1915. A drug may be considered to act directly on the center if emesis occurs with smaller doses and more rapidly when the drug is given by vein than by mouth; and if the phenomena of nausea and the motions of emesis occur after the whole alimentary tract has been removed. According to these criteria, they found that the emetic action of most alkaloids is central; namely, apomorphine, morphine, nicotine, lobeline, aconitine, veratrine, pilocarpine, quinine and ergot; as also picrotoxin, digitalis and sodium salicylate. With ipecac, the local action probably contributes to the result.

Therapeutic Use of Emetics.—These are employed chiefly in acute poisoning, if gastric lavage is not practicable. They are not effective in profound narcosis by chloral or chloroform (Harnack, 1874), barbiturates or other hypnotics, morphine, bromide, and so forth. Apomorphine is quite effective in exposing shamming, but involves some risk. Emesis may also be used to empty the stomach in acute indigestion, especially from overeating.

Minor uses, mainly obsolete, are:

To remove solid bodies from esophagus, pharynx or upper air passages. However, according to de la Paz and Garcia, 1916, emesis does not dislodge solid bodies from the trachea or bronchi, but may drive them deeper. Plugs of mucus may be displaced by increased secretion of mucus. Emesis may cut short an attack of *asthma* (Hoover and Taylor, 1915).

To cause *compression of the liver*, for the removal of bile and small gallstones from the gallbladder and ducts. The usefulness of this measure is doubtful; since the intestines are also compressed, the force cannot be very effective, and on the other hand it might rupture a distended gallbladder.

Contraindications to Emetics.—These are mainly due to increase of pressure and to debility, and are as follows: (1) Severe *heart* *defects*, or *aneurysm* of the aorta, since the sudden and violent increase of intrathoracic and intra-abdominal pressure may result in the rupture of these organs. (2) *Atheroma.* The sudden changes in blood pressure are likely to burst a vessel and produce apoplexy. (3) Similarly, they may lead to hemorrhages in *phthisis*. (4) In *advanced pregnancy* abortion may result. (5) Tendency to *hernia*. (6) In all *debilitated conditions* there is danger of collapse. (7) *Caustic poisoning.*

◆

THE PHARMACOLOGY OF TEMPERATURE REGULATION

In warm-blooded animals, departures from the normal temperature disturb a variety of functions more or less profoundly and set off compensating reactions, partly directly and partly through heat-regulating centers of the midbrain, which tend automatically to restore the normal temperature. Heat production and heat dissipation both have a share in this regulation and balance each other. The automatic compensation or regulation is adequate under ordinary conditions and with normal animals, but it may become inadequate if any of the factors entering into it are powerfully altered, and the temperature may thus rise or fall. The changes usually involve several factors, at least secondarily, which vary with conditions. *Heat production* is largely incidental to the ordinary activities of the animal. Voluntary work or involuntary shivering is used in the regulation of temperature; but the regulation by changes in *heat dissipation* is more rapid and generally less disturbing, and is therefore principally utilized. Heat is lost mainly from the skin and respiratory tract, by radiation and conduction, and by the evaporation from the skin and from the pulmonary surface. The relative importance of these channels of heat loss differs in different animals and in the same individuals according to circumstances. In man, the skin is the chief means of regulating the heat loss. *In fever*, the heat regulation is adjusted to maintain abnormal temperatures, so that it appears as if the "pitch" of the centers could be altered by pathological conditions, just as the respiratory center may be narcotized to maintain a higher level of carbon dioxide; and the effects of pyretics and antipyretics have been attributed to lowered threshold and narcosis of the temperature centers. The actual phenomena, however, are more important than the hypotheses.

Direct Application to Heat Centers.—Heat regulation is markedly affected by the direct application of heat, cold or drugs to the region of the caudate nucleus. The temperature is thus *raised* by cold, corrosive poisons, caffeine or tetrahydronaphthylamine ("tetra"); it is *lowered* by heat, chloral, antipyrine or quinine applied to this region (Barbour and Wing, 1913; Prince and Hahn, 1918). Indeed, the drugs are more effective in this way than intravenously. *Direct heating and cooling of the center* have no influence on the febrile reaction to tetra, epinephrine or large doses of cocaine (sympathetic stimulants); but they modify toxin, salt and anaphylactic fever (Hashimoto, 1915). The antipyretic action of antipyrine and salicylate is markedly increased by heat, removed by cold. Heat is effective after quinine, cold is not. Morphine removes the response to both heat and cold.

Heat production may be *increased* by greater activity of the organs, especially by muscular work, or even by increased muscular "tone." The febrile increase of heat production is due partly to shivering, partly to increased activity of the glands, partly to glycogen mobilization by the liver. The "dynamic action" of proteins plays a minor part. Conversely, the production of heat may be *diminished* by reducing metabolism; by quieting the muscular movements with morphine; by lowering their tone with ether, or paralyzing them with curare; by starvation or by depriving an animal of its glycogen; and by reducing the circulation by vasomotor or cardiac depression (collapse), and so forth. The *importance of the chemic regulation* may be judged by the fact that animals become practically poikilothermal when they are paralyzed by curare (Pflueger, 1878) or by high section of the cord; that glycogen-free animals are not rendered febrile by "heat puncture," and the like. Heat may also be supplied directly by physical means, by conduction, radiation, diathermy and insolation.

Heat dissipation is controlled by three factors: (1) *Blood flow* to the skin, acting partly by favoring radiation, partly by increasing perspiration and therefore evaporation. (2) *Air currents*, especially rapid, shallow breathing, which favors evaporation. This is utilized especially by animals, whose fur interferes with evaporation from the skin. (3) The *water affinity of the blood* and eventually of the tissues. All three mechanisms appear to require the cooperation of the supramedullary (midbrain) centers for their adjustment.

The Role of Evaporation.—Water is vaporized from the lungs by the evaporation of the sweat and by direct evaporation from the cutaneous epithelium (Keeton, 1924). The volatilization of 1 cc. of water abstracts 0.6 calories from the body. In man at rest, evaporation accounts for only the smaller part (one-fourth) of the heat loss; but it is the most rapid method of heat regulation and plays the dominant share whenever *extra* heat loss is required; *i. e.*, in compensation against excessive heat production, or against external heat. It is of especial importance in the production and relief of fever.

The *vascularity of the skin* is especially important in man. It plays a conspicuous part in the protection against external heat or cold; against incidental overproduction of heat in muscular work; in the rise and decline of fever, the "chill" and the "crisis"; and in the action of most antipyretic drugs. The vascular reactions may be evoked by direct action on the vessels, by reflexes from the temperature sensations of the skin, and by temperature or other changes in the thermoregulating centers. The sensations that arise in the skin itself often seem the dominant element in evoking and intensifying the regulating mechanisms. The sensation of cold even when it originates in only a limited area of the skin produces general constriction of the cutaneous vessels, as well as shivering. The ischemia of the skin intensifies the sensation of cold and thus causes further constriction. A sensation of heat produces hyperemia of the skin (and diminished muscular tone). The hyperemia feels warm and so produces more hyperemia. The thermoregulating centers, however, appear to be necessary to accelerate or arrest the reaction at the proper level. *Diaphoresis* tends to parallel the vascularity of the skin; but it is also influenced by the central innervation of the sweat glands (and by autonomic poisons), and by the water affinity of the blood and tissues.

The *heat dissipating mechanism of fur-bearing animals* differs considerably from the human (Dill *et al.*, 1933), involving chiefly *polypnea*, panting, as the temperature rises. The degree depends upon the excitability of the thermoregulating center. Light panting increases the ventilation in cats and dogs six to seven times, and it may rise to twenty-seven times the normal. The CO_2 of the blood falls by 40 per cent in light panting, by 55 to 60 per cent in severe. The oxygen saturation is increased (Anrep and Hammouda, 1932). The carotid body takes a part in this regulation: increase of its temperature increases the respiration rate, cooling causes slowing (Bernthal and Weeks, 1939).

The Blood Concentration as a Factor in Temperature Regulation.—Changes of the water content of the blood affect heat loss in several directions. Concentration of the blood decreases its volume and increases its viscosity, and thereby diminishes the blood flow. It also increases the affinity of the colloids for the water, and thus decreases the rate of secretion of perspiration, and of evaporation. The importance of this factor has been emphasized especially by Barbour, who found a marked parallelism between the body temperature and the concentration of the blood (solids or hemoglobin); *i. e.*, the concentration of the blood rises and its water content diminishes, when the temperature is raised by infective fever, cocaine, "tetra," hay infusion or Shiga vaccine pyrexia, with the onset of the chill (Barbour, 1931). The concentration is restored, *i. e.*, lowered, by antipyretics (salicylates, quinine, antipyrine), which, in the absence of fever, have little effect on either the temperature or the blood concentration (Barbour and Herrmann, 1921). Dilution of the blood by the injection of saline (Barbour and Freedman, 1920) or by the administration of glucose (Barbour and Howard, 1920) also lowers febrile temperature, but does not affect normal temperature. Phlebotomy leads to dilution of the blood, and this may be an effective factor in the old treatment of fevers by bleeding. When it is attempted to change the body temperature by external heat or cold, animals protect themselves against the heat by dilution; against the cold by concentration of the blood (Barbour, 1924).

The *water lost from the blood* goes into the tissues, particularly the liver and subcutaneous tissue. The weight of the liver, for instance, increased 3½ per cent in the chill, and most of this was lost when the temperature was restored by antipyrine (Sherman and Barbour, 1935). With the passage of water into the liver, during the rise of temperature, the *liver glycogen* decreases, forming sugar, which helps to hold the water in the liver. This is largely prevented by denervating the liver (Barbour, 1931). In the dilution of the blood volume by antipyretics, this sugar passes into the blood. The shivering of the chill in the onset of fever increases the lactic acid of the muscles, and this draws water into them and accounts largely for their share in the blood concentration (Barbour and Gilman, 1934).

The Changes of Blood Concentration against External Temperature Require the Thermal Centers.—They do not occur if the animals have been rendered poikilothermal by operations on their central nervous system (Barbour and Tolstoi, 1924), and are abolished by ether narcosis (Barbour and Bourne, 1924). The regulation also fails if the external temperature exceeds a certain degree (for dogs, 42° C. in dry air; 33° C. in moist air). These extreme temperatures produce fever and therefore concentration of the blood and dehydration of the tissues (Lozinsky, 1924). The osmotic pressure response to cold is abolished by ergotoxine (Barbour and Gilman, 1934). *Cold applied to the brain base* causes blood concentration and liver hydration; heating of this region has the opposite effects. Heating and cooling the medulla produce the reverse changes (Barbour and Aydelette, 1933).

REACTIONS WHICH RAISE THE TEMPERATURE (PYRETICS)

Increase of heat production or diminution of heat loss tends to raise the temperature; but a significant rise of temperature, *i. e.*, fever, occurs only if the change exceeds the capacity of compensation, either because it is extraordinarily great or because it involves more than one factor or because the temperature-regulating centers do not function normally. This break in compensation may be caused by a number of agencies, acting through different mechanisms. The most important are the bacterial products of infectious fever. These disturb the heat-regulating centers, chiefly to diminish heat loss, but partly also to increase heat production. Injections of foreign protein, of milk or peptone act similarly. Sympathetic stimulants: Epinephrine, ephedrine, cocaine, tetrahydronaphthylamine and methylene blue increase heat production, but they act chiefly by decreasing heat loss, by decreasing the flow of the blood to the skin, and by increasing blood concentration (Barbour and Gilman, 1934). Dinitrophenol and its derivatives produce fever almost exclusively by increased heat production.

Resistance of Birds to Pyretic Agents.—The temperature regulation of birds differs materially from that of mammals, so that hens and pigeons do not develop fever by the administration of most of the agents that are pyretic in mammals (Barelli, 1932). Milk injection has no effect; tetrahydronaphthylamine actually lowers the temperature, averaging 3°, maximum 5.8°, and with high doses the fall persists for several days. Cocaine and caffeine also lower their temperature (J. Bill, 1936). The blood sugar rises as the temperature falls under tetra; also with morphine, barbiturate and urethane; but paraldehyde produces hypoglycemia (Allen and Brill, 1936).

Therapeutic Use of Hyperpyrexia.—Increase of the body temperature is injurious to some of the micro-organisms of infections; for instance, in the late forms of syphilis, especially neurosyphilis, which do not readily yield to chemo-therapy, but are markedly benefited by fever induced through inoculation with malaria (J. Wagner von Jauregg, 1918), or by hot packs or baths which raise the body temperature to 39–40.5° C., 102.2–104.9° F., for some six hours (Epstein and Cohen, 1935). Heat is also effective against experimental syphilitic infection of rabbits (Weichbrodt and Janice, 1919; Schamberg and Ryle, 1926). Hyperthermia has considerable success against gonococcal infections and various forms of rheumatism. It is not known how much of the effect is directly bactericidal, and how much indirectly.

Stimulation and Destruction of the Heat Regulating Centers.—The *"specific" heat production* (as distinguished from that incidental to physiological activity) is under the control of the central nervous system; the muscular tone, for instance, depends on the spinal cord. The rise of temperature produced by puncture of the corpora striata of rabbits ("heat puncture") is due to increased heat production (Richet, 1895), involving especially the hepatic glycogen, since it does not occur in glycogen-free animals (Rolly, 1903). Muscular heat production is not essential, for the temperature rises also in curarized animals (Hirsch and Mueller, 1903). Walbaum, 1913, however, contended that the chief factor is cutaneous vasoconstriction. When the temperature has risen, there is a partially compensating increase of heat loss. The regular course of the fever, which continues for several days, indicates a regulation, which balances the disturbed functions at the febrile level. This may be lowered artificially, by external cold or by antipyretics, but is promptly resumed when these cease to act (Schultze, 1899). High section of the spinal cord destroys heat regulation completely. Ablation of the cerebral hemispheres has little effect. Traumatic or electric irritation of various parts of the midbrain (particularly the corpus striatum, optic thalamus and the ponto-bulbar junction) produces a rise of temperature (Hale White, 1890); but F. Sachs and Green state that faradic stimulation of the caudate nucleus does not produce any temperature changes, in animals or human.

The Ponto-Bulbar "Center."—Tschedschichin, 1866, observed that the temperature rises when a section is made at the junction of the pons and medulla; the same result follows electric stimulation of this region (Heidenhain, 1870) and irritation of various other parts of the midbrain.

Chemical Changes and Adjustments in Hyperthermia by High External Temperature and Other Physical Hyperthermias.—In human subjects, the heat treatments cause loss of *body weight*, great increase of *fluid intake* and therefore little change in *urine volume*, but increase of the *urinary specific gravity* to 1030 to 1035, returning to 1015 to 1020 when the subject becomes accustomed and adjusted to the heat. *NaCl loss* by the sweat is increased, that by urine decreased; these also return toward normal with adjustment. When the adaptation is completed, the blood constituents are practically normal (Talbott, Edwards *et al.*, 1933; high environmental temperature). The prolonged polypnea causes low *CO_2 concentration* in the blood and alveolar air. The pH of the blood rises to 7.6, that of the urine to 8. The *urinary chloride* concentration becomes low. Free HCl disappears from the *gastric juice*. The *lactic acid* of the blood is high and large quantities are lost by the sweat. The *hemoglobin concentration* is increased, and the *oxygen* is more firmly held, so that its supply to the tissues is diminished (Fishberg *et al.*, 1936; short wave fever). The oxygen content of the venous blood is markedly increased in fever therapy (M. Adams and Boothby, 1936).

The **hyperpyrexia of infections** is central, essentially by diminished heat loss, through contraction of the cutaneous vessels (pallor), concentration of the blood, and arrest of perspiration. The heat production is generally increased, so that the basal metabolic rate, in high fever, may be 40 to 50 per cent above the normal, but this is not essential, and does not exceed the limits which are easily compensated in normal animals.

Altered reaction of the cutaneous vessels is characteristic of fever, suggesting disturbed innervation. They are more easily affected by chemical and mechanical irritation (Baeumler, 1873); they constrict more strongly in response to reflexes (Heidenhain); they are likely to undergo alternate contraction and dilatation, with little apparent cause; a slight degree of cooling produces chilliness, and so forth.

Total Nitrogen Excretion.—Increased nitrogen metabolism is a nearly constant feature of infective fevers, but does not run parallel; it may start before or after the rise, and it generally reaches its maximum after the fever has started to decline. It must therefore be an incidental, rather than an essential, feature of the process, and denotes increased tissue destruction, chiefly by the toxic effects of the infective agents. Simple overheating also increases the nitrogen excretion, but relatively much less than in fever.

Gastric Secretion in the Fever of Infectious Diseases.—The acidity, and its response to histamine, are diminished, parallel to the height of the fever. The volume and chloride suffer a smaller decrease (Chang, 1933).

Heat Regulation in Fever.—The febrile temperature generally runs a more or less regular course, implying control and adjustment to the altered conditions. Adventitious changes affect this adjustment, generally in the same direction as in normal animals, but in different degree.

Fever shows the normal daily variations, the rise during the day, and the fall during the night; although these variations may be smaller or larger than normal. Artificial cooling and heating and the administration of antipyretics provoke the same compensatory reactions as in health, though these are less effective. The febrile temperature can therefore be more easily lowered or raised, and the changes are more extensive and more lasting; but when left to itself, the temperature tends to assume its original febrile level. It might be said that the temperature of fever is adjusted to a higher level (Liebermeister).

Water Fever.—Distilled water is liable to become infected with pyrogenic micro-organisms, which produce fever on intravenous injection of solutions made with the infected water. Careful redistillation is needed to insure freedom from these agencies.

The *pyrogens* formed by various micro-organisms are toxic, nondialyzable substances. They do not contain nitrogen and are probably polysaccharides. They are relatively stable in boiling water, but are destroyed by hydrogen peroxide or potassium permanganate (D. H Campbell and Cherkin, 1945).

Yeast Fever.—Fever convenient for therapeutic studies may be produced in rats by hypodermic injection of a 15 per cent suspension of dried yeast, 10 cc. per Kg. of body weight. It reaches its peak of about 1.5° C. in about sixteen hours and persists more than twenty-four hours (P. K. Smith and Hambourger, 1935).

Foreign Protein Fevers.—The phenomena from the injection of milk, proteose, and the like, are similar to those of infectious fevers. *Irritants* may cause fever by the products of tissue decomposition.

Tetrahydrobetanaphthylamine produces central and peripheral sympathetic stimulation and causes a considerable rise of temperature, in which both increased heat (CO_2) production, chiefly by increased muscular movement, and diminished heat loss, chiefly by cutaneous vasoconstriction, appear essential. The action is not through the temperature centers, for it may be produced after these have been destroyed, and is not antagonized by the antipyretics which act on these centers (quinine, antipyrine, salicylates, small doses of morphine) (Feri, 1911), or by those which cause collapse (peptone, histamine, veratrine); but it is suppressed by dilating the cutaneous vessels by nitrites, chloral or barbital (Anan, 1927); or by producing complete muscular relaxation with chloralose (Regniers, 1928), curare, ether or heavy doses of morphine (Mutch and Pembrey, 1911).

The phenomena were extensively studied by R. Stern, 1889 and 1890; Hale White, 1892; S. Anan, 1927, and others. Waser, 1919, investigated its derivatives.

Dosage and Efficiency.—The subcutaneous injection of 0.04 to 0.05 Gm. raises the temperature of rabbits several degrees, the rise starting in an hour and persisting over four hours; but it fails completely in some animals. Dogs and cats react similarly. In man, nontoxic doses do not produce a rise. In guinea pigs it produces a fall of temperature (Glaubach and Pick).

Other Actions.—Aside from the rise of temperature, it produces dyspnea and restlessness, sometimes convulsions. It wakens even decerebrated animals from chloral sleep—while cocaine and caffeine have this effect only on normal animals (Morita, 1915). It also has important sympathomimetic actions (Jonescu, 1909): stimulation of the cervical sympathetic (mydriasis, exophthalmos); a general vasoconstriction involving both cutaneous and systemic vessels (rise of blood pressure), mainly of peripheral origin (Anan, 1927). It has a moderate peripheral dilator effect on bronchioles (Jackson, 1914). Hyperglycemia occurs only with doses that render the animal restless (Corral, 1918). Elliott, 1914, described the rapid production of gastric ulcers in rabbits from hypodermic injection. In dogs, gastric motility and secretion are depressed for a considerable time by pyrogenic substances in doses which do not raise the rectal temperature (H. Necheles, 1943).

Paranitrophenylethylamine produces prompt and marked hyperpyrexia, with a high degree of blood concentration (Barbour, 1934).

Cocaine hyperthermia is probably analogous to the tetrahydronaphthylamine fever, although some differences have been reported. Increased heat production by restlessness and convulsions may play a larger part (Richet and Langlois); but the loss of body fluid is more severe than in B. coli fever (H. G. Barbour, 1926), indicating greatly diminished heat loss. Cocaine fever may be prevented by curare or chloral, but not by the ordinary antipyretics (Mosso).

Methylene-blue hyperthermia is of short duration, the maximum being reached in an hour, and the return to normal in four hours. Quinine is markedly antipyretic, but antipyrine, amidopyrine, veratrine and chloral have little effect (K. Tokieda, 1927). In rats, the rise occurs only if the animals are placed in warm surroundings, 25° C. or higher (Gregoire, 1931).

Atropine hyperthermia may probably be attributed to the muscular excitement and to the suppression of sweat.

Caffeine Hyperthermia.—Large doses of caffeine produce a slight degree of fever (Binz, 1878; Pilcher, 1911). This could be explained by the increased muscular tone and by the dilatation of the intestinal and consequent constriction of the superficial vessels.

Convulsants.—All convulsant poisons (santonin, picrotoxin, strychnine) produce changes in heat regulation. Small doses cause increased heat loss and a slightly smaller heat production. Larger doses cause increased metabolism, through muscular action, and hence increased heat production, which is accompanied by a further increase of heat loss. Paralytic doses diminish the heat production greatly. The *temperature* is changed, accordingly: Small doses tend to lower it; moderate convulsive doses would increase it; paralytic doses lower it greatly. The heat loss is particularly conspicuous in small and young animals; larger animals tend to show a rise of temperature, with moderate doses (Harnack, 1901). In traumatic tetanus, thermic fever and the like, the temperature may rise greatly, usually when there is a general disturbance of heat regulation.

Dinitrophenol and Dinitrocresol.—Alpha 1, 2, 4 dinitrophenol and related nitro derivatives increase the oxidative metabolism and therefore the heat production chiefly by direct peripheral action. The increase may be pushed to twelve times the normal, in intact mammals, higher than with thyroxin. The larger doses raise the temperature to a dangerous or fatal degree. With therapeutic doses, compensatory heat loss by sweating and faster respiration prevents any temperature rise. The increased metabolism, even when double, involves primarily fat, and practically not the proteins or carbohydrates; nor are the protein metabolites materially altered. The fat is oxidized completely, without producing acidosis or ketones (Tainter, Cutting and Hines, 1935). This oxidation of fat has been utilized for the treatment of obesity, but the drug may cause side actions—frequently skin eruptions and neuritis; exceptionally cataract, neutropenia and liver and kidney damage. These are too serious to justify the use of the drug, although the dangers may be minimized by giving large amounts of water, by increasing the dosage only slowly to a moderate rate of weight loss, and by stopping at the first sign of ill effects. Patients with defective liver or kidney function should be excluded. Dinitrophenol is quite ineffective against thyroid deficiency, except as to metabolic rate. It should not be used for therapeutic production of hyperpyrexia.

Chemistry and Related Compounds.—Most of the investigations have been made with alphadinitrophenol 1, 2, 4. The 1, 3, 6, isomer also increases oxidation. The other four isomers slow oxidation and form methemoglobin (Magne, Mayer and Plantefol, 1932). Extensive comparisons with other derivatives were published by Heymans, 1934, and by Tainter and Cutting, 1933. The most powerful stimulator of cellular oxidation was dinitrocyclo-pentylphenol. This, and some of the others, also had a relatively lower toxicity than dinitrophenol and dinitronaphthol for the digestive tract, liver and kidneys. Clowes and Krahl, 1936, found that the nitro radical is not essential for the direct action on oxidation, for this is also produced by halogen-substituted phenols. However, the halogen compounds had no effect on temperature in intact animals.

Nitrophenols generally (but not orthonitrophenol) tend to be reduced in the organisms to aminophenols (E. Meyer, 1905).

Dinitro-orthocresol was advocated as a therapeutic substitute, especially in England (Dodds and Robertson, 1933). It is about five times as potent, and the dosage is correspondingly reduced (0.5 to 1 mg. per Kg. per day). It is open to the same objections, and has no apparent advantage. Acutely fatal doses of 3-5-dinitro-orthocreso produce increased respiration, hyperpyrexia and early respiratory and cardiac failure. Continued feeding does not materially modify growth or food consumption unless the dosage is fairly high (A. M. Ambrose, 1942).

Historical.—The hyperpyretic and toxic actions of dinitrophenol were described by Cazeneuve and Lepine, 1885. Its toxic hazards to munition workers during World War I prompted renewed investigations, including animal experiments by Magne, Mayer and Plantefol (published in 1931 and 1932). They demonstrated correctly the mechanism of the fever and also showed degenerative changes in the liver and kidneys. Meanwhile, Heymans and Bouckaert, 1928 and 1934, had likewise made extensive investigations, including related nitroderivatives. Tainter and Cutting, 1933, and their associates introduced their use against obesity.

Clinical Doses and Effects of Continued Administration.—The sodium salt of dinitrophenol is generally administered in capsules of 0.1 Gm., with meals, beginning with 0.1 Gm. per day during the first week, then 0.2 Gm. per day for several weeks, observing the response, and then increasing in steps of 0.1 Gm., until the dose is stabilized either by the symptoms of excessive heat and sweating, or by the weight loss (aiming generally at 2 or 3 pounds per week). The diet is limited as far as feasible (Bortz, 1934, recommends 700 to 1000 calories), but fluid is consumed liberally. The average of the treatments (Tainter, Stockton and Cutting, 1935) used 300 capsules of 0.1 Gm. during eighty-eight days, at the rate of 0.34 Gm. per day (the longest treatment was for a year, and 0.6 Gm. was the highest daily dose prescribed, and this for a short period only). The increase of metabolic rate varied rather widely for different patients, but was roughly parallel to the dose, averaging 11 per cent per 0.1 Gm. The treatment caused notable losses of weight in about 90 per cent of the patients, generally even when other methods had failed, and this without severe dietary restriction, and in most of the patients without undesirable symptoms. However, a not inconsiderable proportion show toxic effects, usually rather minor, but some serious. The Council on Pharmacy and Chemistry, 1935 (review and bibliography), warned against its uncontrolled administration.

Direct Increase of Tissue Oxidation.—The rise of temperature is chiefly secondary to the increased metabolism, for it is not prevented by extirpation of the heat-regulating centers (dinitronaphthol in pigeons; van Uytvanck, 1934), nor indeed by destruction of the brain or spinal cord, nor by curare (Tainter, Cutting *et al.*, 1933). Oxidation is increased in isolated cerebral cortex of rats (Fuhrman and Field, 1942). It is increased to three or five times in the arrested heart of turtles (Garrey and Boykin, 1935); in the perfused foot of the dog it may be increased more than three times. This may be inhibited by *cyanide;* methylene blue also increases markedly the oxygen consumption in the perfused foot, but cyanide is a less efficient antagonist (von Euler, 1932). Both agents therefore increase oxidation by direct action on the tissue cells (Heymans, 1932), although dinitrophenol, unlike methylene blue, is not a direct oxidant. In sea urchin eggs, cyanide antagonizes the depressant effect of dinitrocresol on oxidation, but the two are additive in suspending cell division (Clowes and Krahl, 1935). Dinitrophenol is not practically effective against cyanide poisoning in the higher animals (Tainter and Cutting, 1933); nor does cyanide antagonize the toxicity of dinitrophenol for animals, but rather adds to the fatality (van Uytvanck, 1931). Dinitrophenol also stimulates oxidation in *yeast cultures*, but higher concentrations inhibit (Field, Martin and Field, 1934).

Central Pyretic Action.—Although there is no doubt as to the direct, peripheral action of dinitrophenol on oxidation, there is also a central action in the same direction, probably on the midbrain and not on the ordinary thermoregulatory center, and this plays the chief role with the smaller therapeutic doses (3 mg. per Kg.) (Siedek, 1934), although with larger doses it is overshadowed by the peripheral action. In harmony with this, the increase of oxidation is potentiated by epinephrine (V. E. Hall and Chamberlin, 1937).

Relations to External and Internal Temperature.—Dinitrophenol (as also the related pyretic agents, tetrahydrobetanaphthylamine and methylene blue) are much more effective in raising the temperature if that of the surroundings is warm (22° C. or over). *If the external temperature is 16° C. or below*, they do not produce increased oxidation and pyrexia, in mammals or birds; on the contrary, they lower oxidation by greatly diminishing or abolishing shivering and eventually cause rapid cooling of the animal. They therefore disturb heat regulation in both directions, so as to exaggerate the detrimental effects of external temperature (Tainter, 1934; Riddle and Smith, 1935; Fuhrman and Field, 1942). External cold has been suggested as probably the most effective treatment of acute dinitrophenol poisoning; it may double the fatal dose (Tainter, 1934). In *hibernating animals*, these pyrogenic agents are more effective than after awakening, when the temperature has risen (Barelli, 1933).

Carbon Metabolism.—The increased oxidation involves both fats and carbohydrates, in the normal proportions (Hall, Fields *et al.*, 1933). Clinically, fat tends to furnish the larger share of the fuel (Tainter, Cutting *et al.*, 1935; decrease of the respiratory quotient). The nitrogen excretion is not increased.

Hyperglycemia.—Ordinary doses of dinitrophenol cause considerable increase of the blood sugar level, in normal subjects, or after injection of dextrose, but not in diabetes (Wishnofsky *et al.*, 1935). In dogs, it is reported to hasten the passage of injected dextrose out of the blood (Ashe, 1935). The lactate concentration of the blood and muscles also tends to rise, while the glycogen of the liver and muscles is markedly decreased (Magne, Mayer and Plantefol, 1933). The hyperglycemia is not due to asphyxia, for it occurs even when the oxygen content of the blood is normal (Hall, Brown and Sahyan, 1933).

Anoxia.—The increased demand for oxygen leads to faster and deeper respiration, and to increased blood flow; the latter has also been demonstrated in the clinical use (H. Freeman, 1934). Apparently it is due chiefly to muscular vasodilatation, and some increase of heart rate and rise of venous pressure, but with little change in arterial blood pressure (Stockton and Cutting, 1934). The oxygen in the venous blood falls, but that of the arterial blood remains fairly normal, and there is no acidosis so long as the respiration and circulation remain adequate. If the oxygen demands exceed compensation, anoxemia and acidosis develop, with cyanosis, piling up of lactic acid in the tissues, leading to early rigor mortis. The oxygen consumption and the respiration are decreased shortly before death. The high fever may culminate in heat rigor, first in the extremities, and finally in the respiratory muscles (Tainter, 1935; Hall, Field *et al.*, 1933).

Comparison with Thyroxin.—Both agents accelerate oxidation powerfully, at least in part by peripheral action, but dinitrophenol acts immediately, while the thyroxin action develops slowly. Dinitrophenol does not remove the phenomena of hypothyroidism other than the basal metabolism and lacks completely the other actions of thyroxin, the tachycardia and the sympathetic anxiety complex of thyroxin overdosage; and the acceleration of tadpole metamorphosis. Dinitrophenol also fails to change the cholesterol concentration of the blood, which on thyroid administration varies with the metabolic rate (Cutting, Rystand and Tainter, 1934). Dinitrophenol does not increase the basal metabolic rate of rats rendered hypothyroid by thiouracil, suggesting that the metabolic action of dinitrophenol requires thyroid hormone (S. B. Barker, 1946).

Acutely Toxic Effects.—Serious acute poisoning is rare and occurs only with gross overdosage (literature: MacBryde and Taussig, 1935). Anoxemic cyanosis and acidosis do not set in as long as the respiration and circulation remain adequate. They are more to be feared in hyperthyroid patients, in whom the increase of oxidation would be additive. Tainter, 1934, showed that dinitrophenol and thyroid administration both lower the resistance to diminished oxygen tension; and conversely, that oxygen inhalation decreases the toxicity of dinitrophenol. The chief danger in acute dinitrophenol poisoning is *excessive hyperpyrexia*, which may culminate in heat rigor, first in the extremities and finally in the respiratory muscles (Tainter, 1935; Hall, Field *et al.*, 1933). In acute overdosage, death generally occurs within twenty-four hours after onset of the symptoms. Postmortem examination has shown degenerative changes in the liver, kidneys and heart muscle.

The *treatment of acute poisoning* comprises gastric lavage with 5 per cent sodium bicarbonate, leaving a large volume of fluid in the stomach; copious intravenous dextrose; cold pack or tub; oxygen inhalation if cyanosed (Tainter). Antipyretics, chloral and barbiturates do not influence the toxic phenomena or the hyperthermia (Tscherkess *et al.*, 1935). Conversely, *dinitrophenol is not an effective antidote* to morphine, chloral, alcohol or barbiturates, although it may temporarily improve the respiration (Tainter and Cutting, 1933). It is not an effective antidote to alcohol (Newman and Tainter, 1936); nor is it effective against cyanide poisoning in the higher animals (Tainter and Cutting, 1933); nor does cyanide antagonize the toxicity of dinitrophenol for animals, but rather adds to the fatality (van Uytvanck, 1931).

Special contraindications to the employment of dinitrophenol are diabetes, and disturbances of the kidneys, liver and heart. Pancreatectomized dogs are hypersensitive to dinitrophenol and die before the usual febrile responses are fully developed. This may be counteracted by the administration of insulin. Dinitrophenol decreases but slightly the hyperglycemia of pancreatic deficiency, and its administration to diabetic patients would therefore be useless as well as dangerous (Tainter, Boyer and De Eds, 1933). Administration of thyroid with dinitrophenol increases the stimulation of metabolism and loss of weight, but the dangers are even greater (Glaubach and Pick, 1934). *Low-fat diet* renders mice more susceptible to the toxic effects of *dinitrotoluene* (Clayton and Baumann, 1944).

Fatal Dosage of Dinitrophenol for Animals.—The minimal fatal dose for 50 per cent of the animals ranges between 20 and 30 mg. per Kg., for various kinds of animals and methods of administration, and therefore presumably also for man; indeed, all the effects in man resemble closely those of equal doses (relative to body weight) in animals (Tainter and Cutting, 1933). The effects of continued feeding to rats of various concentrations are reported by Tainter, 1938.

Toxic Effects from Continued Administration.—Minor side actions, especially skin rashes, are rather common; severe reactions occur only in a small percentage of patients, but they are the more dangerous, because they are unpredictable and develop insidiously after ordinary therapeutic doses have been used for a short or long time without apparent harm. Because the action on metabolism does not increase with continued administration, the earlier users believed that there was practically no risk if a moderate dosage (0.3 Gm. per day) were not exceeded, and if the increase of metabolic rate was kept within reasonable bounds (less than 50 per cent, Dodds and Robertson); but of the patients who took 0.3 Gm. or more for at least six weeks, 23 per cent showed some undesirable effects, especially skin rashes (23 per cent; 2 severe) and peripheral neuritis (18 per cent) (Tainter, Stockton and Cutting, 1935). Such accidents, and the more serious cataract and neutropenia, continued to be reported in the course of ordinary practice; and although the causative relation is not always clear, it must be feared that any effective dosage may develop harmful consequences. The most common *skin reaction* is rather intense itching (with or without erythema) and urticarial or maculopapular eruptions. They generally subside in two to five days after withdrawal, and may or may not recur on resuming the drug. In two cases, there was severe dermatitis of allergic type (Tainter, Stockton and Cutting, 1935). One such case was shown to be allergic by the Prausnitz-Kuester passive transfer test (Frumess, 1934). There may also be swelling of *mucous membranes. Disturbances of smell and loss of taste*, especially for salt and sweet, are common. *Peripheral neuritis* involves especially the legs and feet. It comes on slowly, and clears up three weeks or longer after withdrawal, or may be quite persistent (Nadler, 1935). Long-continued use seems to lead in some cases to *cataract*, even in young individuals (W. W. Boardman, 1935). By 1942, cataract had been reported in 177 persons, often from the ordinary doses and without other untoward effects. The mechanism is not known (W. D. Horner, 1942). Several cases of *malignant neutropenia* have been reported, all from dosages within the supposedly safe limit. Prodromal symptoms of fever, sore throat and headache set in from ten days to four months after starting the drug, and proceed in one to eight days to pharyngitis, cyanosis, stupor, and sometimes death (S. W. Imerman and Imerman, 1936; Goldman and Haber, 1936). Cases of marked *cardiac disturbances* (arrhythmia, bradycardia, sinus rhythm) have been recorded (de Chatel and Motika, 1934). Functional changes in the *liver*, *heart* and *muscles*, and diminished dextrose tolerance, are claimed by MacBryde and Taussig, 1935, for a large proportion of patients who did not show evidence of special idiosyncrasy, but Tainter and Cutting, 1933, found no indication of liver or kidney injury by functional tests; and Schulte, 1937, also failed to find functional or anatomical evidence of liver injury, or opacities of the lens, in dogs that had received rather large doses for half a year. Warthin, 1918, had shown that dinitrophenol may produce toxic hepatitis and jaundice, similarly to picric acid and trinitrotoluol. Increased number of *stillbirths* and increased mortality of the young has been reported for rats receiving fairly large doses (Wulff, Emge and Bravo, 1935).

Cataract occurs routinely in young *chicks* when 0.25 per cent of dinitrophenol (not ortho or para mononitrophenol; W. C. Dietrich and Beutner, 1946) is added to their feed. Fine vacuoles appear in the anterior lens fibers in four to six hours. The posterior fibers show severe degeneration in three to five days (B. H. Robbins, 1944). Rats apparently do not develop *cataract* when large doses of dinitrophenol are fed from weaning till death, which occurred in thirteen months instead of twenty-four months in the controls. Nor did any other organ show histologic changes (Tainter, 1938); nor did cataract develop when vitamin A and riboflavin deficiency was superadded in rats, and ascorbic acid deficiency in guinea pig (Tainter and Borley, 1938); nor did dinitrophenol sensitize rats in any degree to lactose cataract (Borley and Tainter, 1938).

REACTIONS WHICH LOWER THE TEMPERATURE (ANTIPYRETICS)

The temperature may be lowered by anything which diminishes heat production or increases heat loss. As the temperature tends to fall below normal, compensatory reactions are set up, which ordinarily suffice to keep the temperature at the normal level. Indeed, it is difficult to depress the temperature materially below the normal, except by means which effect profound and extensive changes, such as deep narcosis, general vasomotor paralysis or other collapse conditions. It is relatively easy to lower an abnormally high temperature. Accordingly, the practical antipyretics become such only when the temperature is excessive. They have little influence on normal temperature, because their effects would evoke more powerful compensations and partly also because the primary effects themselves are less powerful when they must overcome a normal state, than when they are assisting an abnormal state to the normal. However, the increased response to antipyretics is not confined to high temperatures, but occurs also in infections when the temperature averages but little above normal, such as chronic tuberculosis, osteomyelitis and empyema (Barbour, 1919).

Action of Therapeutic Antipyretics.—The therapeutically available antipyretics act in several ways: The *application of cold* (baths, and the like) results in the direct abstraction of heat; the *chemical antipyretics, antipyrine, acetanilid, phenacetin, quinine, salicylates,* and so on, increase heat dissipation chiefly by mobilizing water, diluting the blood and thus promoting perspiration, aided by dilatation of the cutaneous vessels. Their action is mainly central. *Nitrites* dilate the skin vessels directly. *Aconite and veratrum* probably lessen heat production by slowing the circulation.

Drug changes of normal skin temperature reflect the vascular changes in the skin and are most marked in the extremities, especially the toes. Bierman, 1936, reported: *Marked increase*, by acetylsalicylic acid. *Increase*, by amyl nitrite, alcohol, thyroid administration. *Initial decrease followed by increase, at site of application,* by irritants (iodine and mustard). The increase may last five to ten hours. *Decrease* by pilocarpine (by evaporation of sweat), smoking, caffeine and coffee. Decaffeinated coffee had no effect.

Relation to Heat Centers.—All the antipyretics depress temperature effectively when applied directly to the caudate nuclei. When the central control is excluded, quinine is still antipyretic, while antipyrine and salicyl tend to raise the temperature (Isenschmidt, 1913; Barbour and Denning, 1913).

Therapeutic Use of Antipyretics.—The reduction of hyperpyrexia gives considerable symptomatic relief in fever and rests the patient. It is especially appreciated in the early stages, before adjustment has been reached. For this, it is not necessary to lower the temperature to the normal level, especially as large doses may cause dangerous collapse. Even partial reduction of the fever may be harmful if the febrile temperature is bacteriostatic. Large doses of antipyretics may also interfere with the production of various types of antibodies in animals (Inoye, 1933), but this has not been demonstrated for therapeutic doses.

◆

QUININE, OTHER CINCHONA ALKALOIDS AND OTHER ANTIMALARIAL DRUGS

The bark of the cinchona tree (Peruvian or Jesuits' bark or Cardinal's bark) has a selective effect on malaria, so that a single adequate dose suppresses the plasmodia in the blood. This action is due chiefly to the alkaloid quinine, but is shared more or less by other cinchona alkaloids, quinidine, cinchonine, cinchonidine, and the like, and by most of the numerous chemical derivatives of quinine, and also by certain benzene derivatives, notably quinacrine (atabrine) and pamaquine (plasmoquine), and to a minor degree by several miscellaneous drugs. Its mechanism is not established. Quinine is a general protoplasmic poison, toxic to all cells and to many unorganized ferments and to the brownian movement of colloids. It is especially toxic to ameboid cells, and relatively nontoxic to higher organisms. It is a fairly effective antipyretic, increasing heat loss by hydremia and by dilatation of the skin vessels. It is useful as an analgetic in colds, and in the form of quinine-urea hydrochloride as a local anesthetic. Through its bitterness, it acts as a stomachic tonic. It may stimulate the uterus. Full doses produce "cinchonism," characterized especially by auditory and visual disturbances, which may assume grave proportions with excessive doses. These also cause renal irritation. Very large quantities have sometimes been consumed without serious poisoning, chiefly because the absorption of the drug is limited. Hypersusceptibility and idiosyncrasies are common. Cinchona also contains considerable tannic acid.

Historical.—Until the middle of the seventeenth century, men were quite helpless against the malarial fevers which ravaged the marshy districts of the world. The tree which yields the quinine grew only in South America, and the Indians generally appear to have been ignorant of its effects against malaria. The several accounts of their original discovery are imaginary.

The first that is known of its therapeutic use is the successful treatment, by someone unknown, of a Spanish official at Loxa, Ecuador, Don Lopez de Canizares, in 1630. He suggested its use to the viceroy of Peru, whose wife, the Countess of Chinchon, was cured by it in 1638. (There seems to be some doubt of this account; A. W. Haggis, 1941.) By the next year, the drug was in use in Spain, and in 1640 it began to make its way through Europe. In 1670, large quantities were imported and distributed by the Jesuit fathers. Its use was opposed by many of the scholastically minded "regular" physicians, who considered it inconsistent with the tenets of Galen; but it received the support of the more enlightened, who gave it a practical trial, especially Sydenham, 1675; and of the "pseudo-medics," such as Robert Talbor, physician to Charles II, 1675, who gained fame and substance by exploiting cinchona as a secret remedy. The cinchona was administered as powder, decoction or extract. The discovery of alkaloids in opium by Sertuerner was promptly followed in 1820 by the isolation of quinine and cinchonine from cinchona, by Pelletier and Caventou. Pasteur in 1853 established the relations of the isomers quinine and quinidine, and of cinchonine and cinchonidine. The collection of the bark entails the destruction of the trees. As the use increased, the native trees of the Andes approached extinction, and attempts were made between 1850 and 1860 to establish cinchona plantations in other countries of suitable subtropical climate, especially in the highlands of Java, British India and Ceylon. The first attempts appeared unpromising, the barks being too poor in quinine; until a new variety, the ledgeriana, was raised from seeds collected in 1865, through Charles Ledger, in Bolivia. This proved especially rich in quinine, but was not sufficiently hardy until it was grafted on stocks of Cinchona succirubra. It has been further improved by selective breeding. The plantations of Ceylon and India have been largely abandoned (M. Kerbosh, Proc. Cinchona Anniversary, Mo. Bot. Garden, 1931; this volume also contains other historical papers on cinchona). The cinchona alkaloids remained the only effective means of treating malaria until 1926, when plasmoquine was introduced by Mühlens. This was followed in a few years by atabrine, an acridine derivative, which rivals or surpasses quinine in effectiveness. *The synthesis of quinine* was accomplished by Woodward and Doering, 1944. More than 14,000 synthetic substitutes were "screened" during World War II, and some give promise of being superior to quinacrine (review, E. K. Marshall, 1946).

The **constituents of cinchona** vary, especially quantitatively, in the numerous species and hybrids, and indeed in individual trees and in different parts of the same tree. The alkaloids are contained in the parenchymal cells in all parts of the plant, probably as cinchotannic glucosides. The bark is richest, especially that of the root. The quinine content of the dried bark may attain 13.5 per cent; commercial bark usually contains 4 to 5 per cent, with about $\frac{1}{2}$ per cent of cinchonidine, $\frac{1}{3}$ per cent of cinchonine, and $\frac{1}{6}$ per cent of quinidine. The mother liquor yields a brown extract, *quinoidine*, containing amorphous alkaloids, chiefly dicinchonicine and diquinidine. It is used as an accelerator in vulcanizing rubber. *Totaquine* is a mixture of alkaloid extract from South and Central American barks which do not contain sufficient quinine for effective manufacture. It is potent against malaria. Aside from alkaloids, cinchona extracts contain a tannin, *cinchotannic acid*, with a derivative, *cinchona red*, both glucosides; soluble organic acids (quinic, and so forth); gum, resin, and so on.

The chemical structure of the cinchona alkaloids is built on a uniform pattern, consisting of (1) a quinoline ring, united by (2) a CHOH (secondary alcohol group) to a (3) quinuclidine ring, "loipon," derived from piperidine. T. A. Henry, 1936, concluded that the plasmodicidal action resides in the quinoline nucleus, and that the remainder of the molecule only serves to introduce the quinoline into the plasmodium. Cinchonine may be considered the parent alkaloid. In the natural alkaloids, the hydrogen in the three position of the loipon is replaced by a vinyl group, which may be substituted by alkyls. The hydrogen in the six position of the quinoline may be replaced by hydroxyl or alkyl-oxyl. In quinine and quinidine, the quinoline bears a methoxy, and the loipon a vinyl group. Changes in these groups cause only rather minor quantitative alterations in the antimalarial efficiency; but this is likely to be destroyed completely by changes in the linking CHOH. The asymmetry of this carbon leads to optical isomers, such as (l) quinine and (d) quinidine; (l) cinchonidine and (d) cinchonine; or (l) ethyl hydrocupreine and (d) ethyl hydrocupreidine. Other isomers, namely, quinicine and cinchonicine, are formed by more drastic chemical rearrangement, involving the CHOH linkage, and, therefore, loss of antimalarial activity.

Colloids and Surface Phenomena.—Quinine, like saponin and proteins, tends to concentrate at the surface of solutions, to form rather rigid films (Ramsden, quoted from Bayliss). These interfere with the condensation of other substances at the surface, and therefore hinder catalytic phenomena, inorganic as well as organic. This may explain the decreased metabolism. The surface action is also shown by arrest of brownian movement; and there is a tendency to precipitate colloidal solutions, such as the proteins. Quinine may therefore produce anaphylactoid phenomena. The quinine film presumably diminishes the permeability of the cell. Quinine tends to arrest cell movements, for instance of the white blood cells, infusoria, cilia, spermatozoa, and others, presumably through the rigidity of its film. All these effects render quinine a "general protoplasmic poison," toxic to all kinds of cells; but its toxicity to vertebrates is relatively low, probably because it is largely bound and deposited in insoluble and harmless form.

Ferments.—Interference with ferment action may be seen in many directions, but is markedly selective (Rona and Reinecke, 1921). For instance, the lipases of the serum, pancreas and stomach are poisoned by quinine, but not those of the kidney and liver. The action is much greater in alkaline than in acid solution. The most important enzyme inhibitions are: the oxydases of blood and of protoplasm autolysis (Laqueur, 1906); slowed acidification of shed blood; lessening of the amount of hippuric acid formed when benzoic acid is circulated through the excised kidney. The various digestive ferments are hindered, but not to the same degree. It lessens the glycogenetic function of the liver; *i. e.*, the postmortem transformation of the glycogen into sugar (Hoffmann, 1877). In the therapeutic administration of quinine, the concentration does not rise sufficiently high to hinder the action of oxydase (Johannessohn, 1919). The effects on invertase and on *paramecia* were studied by Rona and Bloch, 1920.

Hemoglobin shows a characteristic change with strong quinine solutions (Marx, 1906). Neither acid hematin nor methemoglobin is formed; vuzin has a similar action (Bijlsma, 1920; Lewin, 1909).

Action on Leukocytes.—A solution of 0.5 to 1 in 1000 is sufficient to inhibit the movements of *leukocytes* on the warmed slide, and a somewhat larger dose causes their disintegration. Phagocytosis is hindered by 0.001 per cent (Hamburger and Hekma, 1908), but stimulated by low concentrations (Manwaring and Ruh, 1907). The depressant action is observed in *intact frogs* in a classic experiment of Binz, 1867. When the mesentery of this animal is exposed, leukocytes in active motion are seen inside and outside the vessel. If quinine is now applied, the movement of the cells outside the blood will be arrested, while those in the blood stream still emigrate. The result is an accumulation of cells about the vessel wall. If the quinine is injected into the vessel, the reverse takes place. The movement of the cells in the blood is arrested, preventing emigration, while those outside do not come into contact with the poison, continue to move away, and leave a clear zone about the vessel. This action does not occur in mammals, since the necessary dose would kill the animal. *In man and mammals,* it causes at first an increase of the lymphocytes, these being pressed into the circulation by the muscular contraction of the spleen and lymph glands. This is followed after an hour by a decrease, and this is again succeeded by rather marked leukocytosis. Continuous administration leads to leukopenia followed by leukocytosis (G. B. Roth, 1912; Johannessohn, 1919). The *opsonic index* is slightly increased in man by doses of 15 grains (T. B. Wilson, 1907).

Local Actions.—Quinine produces some local irritation and anesthesia. When given hypodermically it occasions severe pain, and may lead to *abscess formation.* When given by the stomach, large doses cause *gastralgia, nausea,* vomiting and diarrhea. It also retards the *absorption* of salts, and probably of food. Its excretion through the kidneys may give rise, with large doses, to *albuminuria and hemoglobinuria.* The hemoglobinuria of severe malaria (black-water fever) may be partly due to increased sensitiveness to quinine.

Ulcers.—The sulfate has been used as antiseptic, styptic and stimulant dusting powder on ulcers.

Sunburn Prophylaxis.—Quinine sulfate is protective through its fluorescence, which transforms the ultra-violet rays into longer non-erythemagenic radiations.

Quinine as Anesthetic.—Quinine and its derivatives, when brought in contact with sensory nerves, produce local anesthesia. This is used clinically in the form of the more soluble and less irritant double salts, especially quinine urea hydrochloride. The anesthesia is more lasting than with other local anesthetics; it may persist for several days (Hertzler *et al.*, 1909). It is indeed due to necrosis of the axis cylinders and sheaths

(R. Salm, 1940), with subsequent regeneration. Concentrations above ¼ per cent sometimes produce considerable irritation, edema and fibrous indurations, and above 1 per cent there may be sloughing. Its employment has therefore greatly diminished (E. Mayer *et al.*, 1920), although some clinicians consider these fears exaggerated (E. J. Brown, 1920).

Quinine-urea hydrochloride is injected hypodermically, generally as ¼ per cent, sometimes 1 to 3 per cent. Solutions of 10 to 20 per cent may be used on mucous membranes. Quinine bisulfate, 2 per cent, has also been used in tonsil and throat operations. Data on the *relative anesthetic efficiency* are given by Sollmann, 1918. The anesthetic effect of cinchona alkaloids for the *cornea* was investigated by Morgenroth and Ginsberg, 1912; literature, Bijlsma, 1920. The local anesthetic action of quinine derivatives is proportional to the protoplasmic toxicity (W. E. Dixon and Premankur, 1927).

Double Quinine Salts.—The increased solubility of quinine hydrochloride (3 parts) by antipyrine (2 parts) was announced by Triulzi, 1892, and Santesson, 1897. Gaglio, 1903, and Giemsa, 1908, advised the urethane compound as being less acid and less readily decomposed by boiling, than is the urea salt (Filippi, 1912). It is made with 1 Gm. of quinine hydrochloride, 0.5 Gm. of urethane, and 2 cc. of water.

Antiseptic Action.—Bacteria and yeasts are killed by quinine, but require a higher concentration (2 to 8:1000) than do the protozoa. The efficiency is not materially hindered by serum or pus (K. Taylor, 1915). It is especially potent against pneumococci *in vitro* (O. H. Brown, 1912; Cohen, Kolmer and Heist, 1917), but is surpassed by ethylhydrocupreine (*optochin*). Other hydrocupreine derivatives, eucupine and vuzin, are potent wound antiseptics.

Antiseptic Irrigations.—The following concentrations of quinine hydrochloride are usually employed: cystitis, 0.05 to 0.5 per cent; conjunctivitis, dysentery, 0.5 per cent, gonorrhea, to 5 per cent; hay fever, spray, 1 to 2 per cent.

Wound Infection by Gas Bacillus.—K. Taylor, 1915, recommended dressing with 0.1 per cent of the acid hydrochloride.

Pneumonia.—There is no evidence that quinine reduces the infection; but full antimalarial doses give considerable symptomatic relief (S. S. Cohen, 1911, 1913), presumably through antipyresis and analgesia. It was advised in *Asiatic cholera* (Fullerton, 1896; Ussher, 1906), where it might check the bacteria in the intestinal lumen; but it appears to have been abandoned. Its administration in *rabies* (Moon, 1913, 1915) is useless (Krumwiede and Mann, 1916; Fielder, 1914 and 1916).

Effect on Digestion.—Small doses of quinine (0.05 Gm., 1 grain), taken before meals, act as a stomachic and tonic, but they are probably inferior to other bitters. Larger doses diminish gastric secretion (Klocman, 1912) and interfere with the ferments and with absorption; even small doses when long continued lessen the utilization of food (but the intestinal *absorption of insulin* is increased by quinine; Hanzlik and Cutting, 1941; Driver and Murlin, 1941). Toxic doses stimulate the vomiting center (Eggleston and Hatcher, 1915). Comp. Tinct. Cinchona (5 cc., 1 ʒ) adds the stomachic effect of aromatics and alcohol, and the astringent action of tannin. It may be useful in chronic gastric catarrh.

Quinine on Normal Metabolism and Temperature Regulation.—These are but little affected by ordinary doses, equivalent to 2 Gm. in man. Larger doses lower the temperature, sometimes with a preliminary rise. With toxic doses, the fall is proportional to the collapse.

Heat production and CO_2 production with 20 mg. per Kg. may be slightly increased by restlessness, but this is compensated by increased heat loss; indeed, the latter tends to predominate. Doses above 60 mg. per Kg. lower the heat production, and increase the heat loss (Hardikar, 1925). The *blood sugar level* is lowered in the human, normal and diabetic, by intravenous injection of 0.5 Gm. (A. Loew and Pfeiler, 1927). The *nitrogen metabolism* is not definitely altered even by fairly toxic doses, in man or animals (B. Rosenthal and Lipschitz, 1926). Injections may produce a temporary increase, probably by the local injury. *In vitro or excised organs*, metabolic processes may be altered by quinine, but presumably the concentrations are much higher than those in the circulation. It depresses the *hippuric acid synthesis* in perfused organs, lessens the oxidation of excised muscle (Senta, 1908), and decreases the autolysis of liver pulp (as also eucupine; Rosenthal and Lipschitz, 1926).

Antipyretic Action.—The suppression of malarial fever by quinine is etiologic. However, quinine also reduces other febrile temperatures to normal, analogous to the other antipyretic drugs, *i. e.*, by adjustment of the temperature-regulating centers, primarily through increased heat loss, assisted somewhat by diminished heat production (Virchow, 1927). The increased heat loss is accomplished partly by cutaneous vasodilatation, but probably chiefly by lowering the excessive concentration of the blood, and this in turn by hyperglycemia (Barbour and Herrmann, 1920). The *clinical antipyretic dosage* is 0.3 to 1 Gm., 5 to 15 grains. Because of the cinchonism, and the occasional idiosyncrasies, its use is restricted largely to conditions in which the depressant action of the ordinary antipyretics is especially feared (influenzal pneumonia or cardiac decompensation), and to colds, in which small doses suffice. Like other antipyretics, it is more effective when the temperature tends naturally to fall; the slow absorption delays the response for an hour or two.

Older Views of Antipyretic Action.—It was formerly held that quinine acts radically different from the other antipyretics, almost exclusively by limitation of heat producton (Gottlieb, 1891), through direct decrease of protiin catabolism. This has been contradicted by all modern workers. It was based partly on data obtained by inadequate methods, partly on the unjustified transfer of highey artificial conditions.

Metabolism.—Gaseous metabolism is but little changed by quinine; there may be a small decrease or increase (Hardikar, 1925; Virchow, 1927). The nitrogen metabolism is also unchanged (Hardikar, 1924).

Efficiency Against Experimental Fevers.—Quinine prevents or reduces the hyperthermia of coli injection, and of heat puncture, but not of tetrahydronaphthylamine (Girndt, 1929). It lowers temperature, if the external temperature is high (Lewitzky, 1869), presumably by evaporation; and after high section of the spinal cord (Naunyn and Quincke, 1869), probably by collapse rather than by antipyresis.

Eucupine and *vuzin* are not antipyretic, but tend to raise the temperature by increased protein metabolism (Rosenthal and Lipschitz, 1926).

Use of Quinine in Colds, Headaches and Neuralgias.—Like other antipyretics, quinine has an analgetic effect in these conditions. It is used in doses of 0.05 to 0.2 Gm., 1 to 3 grains.

Administration of Small Doses.—Small doses of quinine sulfate or hydrochloride may be administered in the forms of pills or capsules; or in solution, the taste disguised by glycyrrhiza (no acid must be prescribed with the latter!). The free alkaloid is almost tasteless, and the tannate should be quite so, because of their slight solubility. Their absorption may not suffice for large, but is probably adequate for small, doses. They can be placed dry on the tongue and swallowed with a draught of water.

The *esters of quinine* with various acids are insoluble and therefore tasteless. They pass the stomach unchanged, but are slowly saponified in the intestines, in this way exhibiting a gradual and presumably weak action. They are more easily administered, and produce less side actions, but are not always devoid of cinchonism. They are used in the same doses as quinine, in powder or suspended in liquids. To this type belong *aristochine* (diquinine carbonic ester) and *euquinine* (quinine ethyl carbonic ester).

Central Actions.—The effects are not important, except with toxic doses. They consist in *slow general* paralysis probably preceded by stimulation, but the latter is difficult to make out in mammals. *Frogs* show increased reflex irritability, followed by loss of spontaneous movement, then paralysis of respiration, and lastly of the cord. The effect on spinal reflexes is discussed by Bijlsma, 1920. The depressing effects are much less marked in *mammals*, but *appreciation of pain* is distinctly diminished. Its addition to morphine or urethane does not increase their narcotic effect. *Mental efficiency tests*, in man, showed marked impairment after 1 Gm. of quinine (Muensterberg, 1892).

Respiration.—Therapeutic doses have no definite effect. Toxic doses stimulate the respiratory center. If the vagi are intact, the respiration becomes fast, but shallow and therefore inefficient. If the vagi are divided, the respiratory volume is increased to such an extent as rapidly to lower the alkali reserve of the blood to a fatal level (Sagata and Tatum, 1923).

Skeletal Muscle.—Quinine, quinidine, cinchonine and cinchonidine have similar actions: Dilute solutions cause direct depression with prolonged refractory phase (details under quinidine). Concentrated solutions produce rigor (literature, Bijlsma, 1920).

Small doses of quinine (5 to 40 mg. of the hydrochloride, intravenously, per Kg. in mammals) increase the tension response to single maximal stimuli, in normal, curarized and denervated muscle. Somewhat larger doses diminish the ability to maintain tetanus, by increasing the refractory period. The excitability of the motor end plates is lowered. Physostigmine and veratrine no longer give repetitive responses to a single stimulus. The response to acetylcholine is hindered or abolished (Oesterle and Maaske, 1939; A. M. Harvey, 1939; A. Ravin, 1940).

Quinine promptly suppresses the myotonus in congenital and atrophic *myotonia*, in torticollis, and in "night cramps" of the extremities; the effect usually lasts only so long as the quinine is being administered (0.2 to 0.5 Gm., by mouth, two or three times daily; A. Wolf, 1936; H. K. Moss and Herrmann, 1940). The result is attributed to the curare-like action (Harvey, 1939). The effect may be obtained within three minutes by intravenous injection. *In myasthenia gravis*, quinine increases the asthenic symptoms, sometimes to a dangerous degree. It may be useful for diagnosis of mild cases, in conjunction with the inverse effect of prostigmine (A. M. Harvey and Whitehill, 1937).

Circulation.—The actions of quinine, quinidine and cinchonine, and presumably of the other related alkaloids which have been less studied, are generally similar, but they differ in practical importance. Quinidine should be consulted for details of the cardiac actions used in the control of auricular fibrillation. With quinine, the circulatory effects are important as side actions of its clinical use in malaria; the vascular action and the antagonism with epinephrine may also be discussed in this place. *Moderate clinical doses* by mouth have little if any effect on the heart or blood pressure. Small doses may produce a temporary quickening of the pulse and rise of blood pressure (references, Bijlsma, 1920). Flushing of the skin and the tinnitus indicate some vasodilatation. *Larger doses*, from 1 Gm. up, in man, tend to lower the blood pressure and to depress the heart. The latter becomes marked with doses of 6 to 8 Gm. (Meldolesi, 1926). *Intravenous injections* cause sharp and often dangerous fall of blood pressure, clinically as well as experimentally, the degree and duration increasing with the rapidity of the injection, as well as with the dose (Bramachari, 1922). The fall of pressure involves *several mechanisms*, especially direct cardiac depression; diminished responsiveness of the vagus; direct depression of the vessels, especially in the skin and muscles; and with intravenous injections, presumably flocculation and shock.

The *prothrombin* level of the blood is lowered materially by therapeutic doses of quinine sulfate (0.33 Gm. daily for 6 to 16 days). This may be avoided by the concurrent administration of K vitamin (L. A. Pirk and Engelberg, 1945).

In dogs, intravenous injections of 10 cc. of 0.1 per cent solutions of *quinine, quinidine* or *hydroxyethylcupreine* have no appreciable effects on the heart rate and respiration. The fall of pressure is greater with quinidine than with quinine (Kruse, 1939).

Cardiac Depression.—This consists in diminished tonus, excitability and force, and in prolonged refractory period, with intact or perfused or atropinized heart (Hammet, 1927; see also quinidine). The heart is also rendered progressively irresponsive to vagus stimulation, electrically or by veratrine (Nelson, 1927). Very dilute solutions may stimulate the heart, especially with unfavorable ion mixtures in the perfusion fluid (W. Burridge, 1928).

Vascular Effects.—The flushing of the skin and ears which accompanies the fall of pressure indicates a specialized vasodilatation. Oncometric measurements on animals indicate that this is confined chiefly to the skin and limbs. The observation that the acute quinine fall is less if the aorta has been clamped at the bifurcation indicates that this vasodilatation is the major element in the fall (E. E. Nelson, 1927). The vasodilator action appears to be directly on the vessels, in mammals; for although frog vessels may be constricted by quinine (Biberfeld, 1918), perfused mammalian organs are generally dilated (Tamino, 1927); and they fail to respond, *in situ*, to stimulation of constrictor nerves or to epinephrine (Nelson). The response of perfused kidney vessels to epinephrine is also impaired; on excised arterial rings this may be observed with dilutions of 1:80,000. The constrictor action of barium is not antagonized (Nakano, 1927). Perfusion of frog vessels with quinine also destroys their constrictor response to epinephrine (Stake, 1929, claimed that epinephrine may even become dilator, which is denied by Santesson), and to veratrine, but not to barium (Kondo, 1919).

Antagonism to Epinephrine.—McCarrison and Cornwall, 1919, were the first to report that epinephrine does not effectively antagonize the circulatory depression of quinine; this holds also for quinidine and cinchonine (Arrilago *et al.*, 1921). Conversely, the cinchona alkaloids diminish the pressor response to epinephrine (Clerc and Pozzi, 1920), repeated doses of quinine increasing the interference. This is probably due chiefly to the direct vascular antagonism. The heart is not concerned, for quinine does not prevent the augmented response of the heart to epinephrine (Hammet, 1927; Nelson, 1927); on the contrary, it tends to prevent the epinephrine slowing (Clerc and Pozzi), both by diminishing the rise of pressure, and by rendering the heart refractory to vagus control.

The **use of quinine as abortifacient and oxytocic** has some traditional but rather undeserved reputation. Clinical doses produce little or no effect unless labor pains have started; it is, therefore, ineffective for inducing premature labor. Abortion has sometimes followed toxic doses, but presumably as a manifestation of the general toxicity, rather than through direct uterine action. It has been claimed that the administration of 0.65 Gm., 10 grains, of quinine, preceded by 2 ounces of castor oil, induces labor at term and hastens uterine involution (Bailey, 1926); but if so, it is probably ascribable to the castor oil; for in malarial districts, quinine is administered freely in all stages of gestation, apparently without terminating the pregnancy. It has been claimed that it is successful only if the os is already partly dilated.

Quinine is also administered to intensify weak puerperal contractions (0.25 to 0.5 Gm. every hour, to a total of 1 Gm.; Franz and Katz, 1921); and as a part of colonic ether anesthesia technic, to offset the depression of the ether. Graphic registration shows little if any effects (Dodek, 1932). The effectiveness is not improved by *intramuscular* or *hypodermic injection*, and these may produce sloughing. *Intravenous injection* (0.5 Gm.) has been used, but the risk is scarcely justified. In the *Gwathmey colon anesthesia*, 0.65 Gm. of quinine hydrochloride is added to the ether-oil mixture, with the hope of counteracting the depressant action of ether on the uterus. In view of the poor absorption of quinine from rectal injection, it appears improbable that it could have this action, unless through local irritation. The absorbed quinine passes into the *fetal circulation*, and the fetus is said to excrete it rather slowly (Dilling and Gemmel, 1929).

Experimentally, moderate doses of quinine may stimulate, and high doses depress, the rhythmic contractions and tonus of the uterus, excised and in situ. The stimulant action increases with the excitability of the uterus in the progress of pregnancy, so that 0.5 to 2 mg. per Kg. induce labor in puerperal cats (Schübel, 1928); but the response is highly variable and often absent. Several investigators report that quinine *sensitizes the uterus to oxytocin,* so that only $\frac{1}{10}$ to $\frac{1}{4}$ of the ordinary dose suffices to produce uterine contraction (Schübel, 1931; Legiehn, 1932).

Excised Uterus.—The stimulant action was described by Kurdinowski, and by Kehrer, 1906. The response varies for different animals and increases with pregnancy (Senta, 1912). In general, stimulation or reinforcement of the movements begins with 1:150,000 to 1:100,000. Relaxation and paralysis occur with 1:10,000 to 1:5000 (Lieb, 1914; Stake, 1929).

Antagonism to Epinephrine Stimulation.—Chistoni, 1922, found that high concentrations of quinine (1:5000) suppress the stimulant effect of epinephrine on the excised uterus of pregnant rabbits. This has been confirmed also for lower concentrations of quinine, 1:100,000 to 1:30,000, which are ordinarily stimulant (Langecker, 1926). Quinine may even render the epinephrine depressant (Stake, 1926, 1929). With the virgin uterus of the cat, quinine exaggerates the depressant response to epinephrine (Nelson, 1928).

Other Antagonisms and Synergisms.—Antipyrine and urethane increase the depressant action of quinine; amidopyrine potentiates the stimulation with small, and the depression with large doses (Kubota). Barium stimulation tends to overcome quinine depression (Stake, 1929).

Cinchonine, cinchonidine and *quinidine* act similarly to quinine (T. Stake, 1926). The dextrorotatory isomers are more oxytocic than the levo (Chopra, David and Dikshit, 1928). *Vuzin* and *eucupine* are ineffective (Bijlsma, 1920).

Other Smooth Muscle.—The *spleen* and *intestines* may be contracted. High concentrations (1:5000 to 10,000) may relax the intestines (Biberfeld, 1916). Excised *tracheal muscle* is relaxed (Trendelenburg). Quinine and quinidine dilate the bronchi *in vivo* (literature, Bijlsma, 1920).

Thyroid Gland.—Hyperthyroid patients are markedly resistant to cinchonism. Administration of quinine, 60 mg. per Kg. daily for several weeks, has no effect on the normal thyroid; but produces regressive histological changes in rabbits with compensatory thyroid hypertrophy (not in guinea pigs). In human exophthalmic goiter, treatment with 2 Gm. of quinine per day had no beneficial effects (Bromberg and Gray, 1931).

Quinine Test for Hyperthyroidism.—I. Bram, 1935, reported that the tolerance for quinine is in direct proportion to the basal metabolic rate, and responds with this to treatment. Patients with high B.M.R. may take 2 Gm. of quinine per day for weeks without cinchonism; up to 6 Gm. per day were given. Only 5 per cent of some 4000 hyperthyroid patients reacted with cinchonism, either because they were hypersensitive, or because their goiter was atypical.

Egg Production.—Quinine, when fed to doves, reduces the size of the yolk and albumen of the eggs. This continues for some time after the administration is stopped, and is then followed by a compensatory increase (Riddle and Anderson, 1918).

Cinchonism.—The larger therapeutic doses of quinine produce headache, ringing in the ears, and disturbed vision, a complex of symptoms grouped under the name of cinchonism. These are probably due to a selective action on the vessels of the eye and ear, which can also be demonstrated experimentally on animals. Toxic doses produce *photophobia, deafness* and *blindness,* at first partial, later complete. Similar phenomena occur with salicylates and related drugs, as indeed also with fever itself, and with "colds." Cinchonism is more easily produced in some individuals than in others. It is said that the minor symptoms may be somewhat diminished by bromides. Hyperthyroid patients generally have marked tolerance for quinine, and absence of cinchonism has some diagnostic significance.

Functional changes of vision and hearing set in promptly. Decrease of visual acuity, and especially of dark adaptation, may be demonstrated ten minutes after oral administration of 0.6 Gm. of quinine. Diminished auditory discrimination may be established by tuning fork in fifty minutes, and subjective auditory sensations persist for five to six hours (Lazarev and Balikov, 1930). Macht *et al.*, 1919, claimed that small doses of quinine increase the acuity of hearing.

Quinine amaurosis occurs in some patients from a single small dose, in others only after prolonged administration or after a single large dose (J. N. Evans, 1923). It is characterized by gradual constriction of the visual field, with dilated, fixed pupils. The fundus in most cases shows spasmodic closure of the retinal artery, some dilatation of the veins, intense retinal edema (Harnack, 1912). The retinal ganglion cells and the optic nerve undergo rapid degeneration (Druauld, 1902), presumably by the ischemia. (Amblyopia may occur, however, even when a scleral fistula is made to counteract ischemia; R. Knoblock, 1946.) Most cases recover with some loss of the peripheral field, but in some the blindness is permanent. Nitrites give striking improvement and perhaps hasten recovery (Pelner and Saskin, 1942). *The internal ear* is found congested, post mortem (Kirchner). Congestion of the tympanum was found in some patients who had taken 5 to 10 Gm. of quinine for attempted suicide (Chryssicos and Yanoulis, 1938). Wittmaak (1903) claimed that the aural congestion is not due to quinine, but to death. He demonstrated changes in the cells of the spiral ganglion, by the Nissl stain and is therefore inclined to attribute the auditory effect to a specific toxicity of quinine to these cells.

Major Toxic Actions of Quinine.—With high doses of quinine, the symptoms of cinchonism are accompanied by *difficulty of speech, confusion of ideas and somnolence, followed by loss of consciousness,* alternating with *delirium, coma,* and at times *convulsions.* The *treatment* is by evacuation and symptomatic.

General paresis may appear, preceded by general depression and muscular weakness. The final symptoms are those of *collapse,* due to general paralysis of the central nervous system, and in part also of the heart. The *respiratory center* shows a short primary stimulation followed by more marked paralysis. This latter is the usual *cause of death.* But since the medullary centers are not markedly affected until late, large doses are often survived. The *fatal dose* is usually given as 8 Gm., but 30 Gm. have been recovered from. It is doubtful how much of this really entered the circulation, since the sulfate is rather insoluble, so that a large amount may not have been absorbed.

The *minimal fatal dosage* of quinine for different animals, hypodermically, was compiled by Bijlsma, 1920. The minimal lethal dose of quinine, quinidine and related alkaloids for guinea pigs was reported by Dawson and Harms, 1934.

Visceral Degenerations.—Cornwall, 1920, administered quinine to rabbits, hypodermically or intravenously, over long periods. He found damage to the epithelium of the suprarenals and kidneys, and increased disintegration of red corpuscles in the spleen. These observations require confirmation.

Purpura hemorrhagica is a not infrequent phenomenon of intolerance after large doses (van der Horst, 1918).

Skin Eruptions and Idiosyncrasy.—Scarlatinal or urticarial rashes are not rare after therapeutic doses of quinine, and susceptible individuals may develop dangerous edemas of the mucous membranes and serious collapse. Local reactions are also produced by the application of quinine solutions (1:1000 to 1:10) to the scarified skin of hypersusceptible patients, while normal individuals do not react, so that this may be used as a harmless test of quinine idiosyncrasy. If this is positive, quinidine may be tested, for while the skin reactivity often extends to the other levo cinchona alkaloids, cinchonidine or ethylhydrocupreine, it extends more rarely to the dextro isomers, quinidine, cinchonine, ethylhydrocupreidine (Dawson and Garbade, 1930, 1933).

Desensitization was partly confirmed in the cases of O'Malley and Richey, 1919, with parallel changes in the skin reaction. Further confirmation is desirable. They started with the oral administration of 5 mg. of quinine bisulfate plus 0.5 Gm. of sodium bicarbonate; after one and one-half hours they gave 0.5 Gm. of bicarbonate with 0.1 Gm. of quinine. This was repeated daily, leaving the desensitizing dose at 5 mg. and increasing the second dose by 0.1 Gm. every day.

Absorption.—Quinine is absorbed mainly from the small intestine (MacGilchrist). The absorption is materially hindered by gastro-intestinal irritation, vomiting, diarrhea and the like (Porak, 1918), but not by dysentery (Chopra *et al.,* 1934). The disulfate is absorbed five or six times more readily than the sulfate from isolated intestinal loops (J. C. Andrews and Anderson, 1943).

Fate.—The greater part of the administered quinine is destroyed in the body. The destruction involves usually 60 to 70 per cent and sometimes to 90 per cent of the quinine (Porak, 1918; Hartmann and Zila, 1918). Less than 10 per cent is excreted after intravenous injection (Taggart *et al.,* 1946).

A large part of the quinine is rapidly removed from the blood in the liver, whether it is administered by mouth, or intravenously, or perfused through the excised liver (Grosser, 1908). It is also destroyed *in vitro* by certain liver extracts. An enzyme has been isolated, associated with flavoprotein liver aldehyde oxidase, which oxidizes quinine, its derivatives, and a variety of quinolines, isoquinolines and substituted pyridines (W. E. Knox, 1946). Excision or chloroform injury of the liver decreases the destruction of quinine and so prolongs the blood concentration and increases the urinary excretion (C. E. Anderson *et al.,* 1943). However, G. Chen and Geiling, 1944, report that hepatic injury or blockage of the reticulo-endothelial cells does not materially alter the rate of disappearance of quinine and quinacrine from the circulation. They consider the lungs chiefly responsible for the removal and enzymatic destruction of quinine. Because of the rapid removal, the toxicity on intravenous injection increases materially with the speed of injection (S. Weiss and Hatcher, 1927). A part, however, is not destroyed, but is fixed, for the lungs, liver, kidneys, heart and brain store it in concentrations greater than in the blood (R. A. Hatcher and Weiss, 1926). The distribution of quinine in the tissues of fowl is described by F. E. Kelsey *et al.,* 1943, using a micromethod of Kelsey and Geiling, 1942, quantitative for 0.1 gamma. B. B. Brodie and Udenfriend, 1943, used a fluorescence method for plasma, available also for quinidine. The **photodecomposition** of quinine was studied by Kyker and Cornatzer, 1943.

The concentration of quinine in the blood plasma varies considerably for the same oral dosage. With the daily dosage of 0.3 Gm. it ranges from 0.2 to 0.9 mg. per 100 cc.; with 0.2 Gm. it averages 0.3 mg.; for 0.5 Gm., 0.5 mg.; for 1.5 Gm., 1 mg. (J. V. Taggart *et al.,* 1946). It is necessary to maintain approximately 0.5 mg. for four days to secure the disappearance of the malaria parasites for fourteen days in blood-induced vivax infections; with 0.4 mg. their suppression is only temporary (R. W. Berliner *et al.,* 1946). Concentrations above 1 mg. are highly toxic (Hartmann and Gila, 1918).

With oral administration of a single dose of 0.5 Gm. of quinine dihydrochloride, the maximal concentration, averaging 1 mg., is reached in half an hour; after twenty-four hours it has fallen to 0.15 mg. (Chopra, Roy and Das Gupta, 1931). *A single dose of the principal cinchona alkaloids,* 10 mg. per Kg., to normal individuals gave the following average peak concentration in mg. per 100 cc. of plasma: quinine, 0.3; cinchonidine and quinidine, 0.2; cinchonine, 0.05. The peak is markedly lower if the alkaloids are administered immediately after a meal (E. P. Hiatt, 1944). Similar results are reported by Taggart *et al.*, 1946. They conclude that the low level of cinchonine is probably due to greater destruction.

After intravenous injection, the concentration falls promptly to about the same level as is attained with oral administration (J. P. Morgenroth, 1918; Hatcher and Gold, 1927).

With quinidine, 95 per cent has left the blood within five minutes, 99 per cent within an hour (Weiss and Hatcher, 1927). Chopra *et al.*, 1934, found the average concentration of 1.2 mg. per cent fifteen minutes after intravenous injection of 0.5 Gm. of quinine dihydrochloride in man, which is slightly higher than with the same dose by mouth; but the concentration was not so well maintained for intravenous injection, so that none could be demonstrated in the blood in twenty-four hours.

Intramuscular injection gives about the same concentration, but it is attained more slowly. Chopra *et al.*, 1934, after 0.5 Gm. of quinine dihydrochloride, found that the maximum (averaging 0.95 mg. per cent) was not reached until after two hours. After twenty-four hours, the concentration was 0.2 mg. per cent.

Partition of Quinine between Serum and Corpuscles.—The concentration of quinine within the corpuscles is about the same as in the plasma (O. S. Gibbs, 1928), or smaller, ½ to ⅓ (Ramsden, Lipkin and Whitley, 1918). *In vitro*, the addition of ethyl urethane increases the ratio in the corpuscles (di Mattei, 1930).

Excretion.—Quinine is excreted mainly by the urine, and somewhat by the feces, even after parenteral administration. Traces are found in other secretions, including the milk (Terwilliger and Hatcher, 1934).

With 1 to 2 Gm. per day, the concentration in the urine is about 600 mg. per liter; *i. e.*, more than sixty times as much as in the blood. The amount recovered from alkaline urine is only half as large as from acid urine, owing to reabsorption of the basic alkaloid from the bladder (Haag *et al.*, 1943; J. C. Andrews and Cornatzer, 1944). Quinine is always present in the gastric and intestinal content after hypodermic injection, in man and in animals. Its appearance in the bile and saliva is irregular (Hartmann and Zila, 1918; Bauer *et al.*, 1918; Valdiguié and Lacaze, 1919).

Course of Excretion.—The urinary excretion begins within half an hour, and is practically completed in twenty-four hours (Nishi, 1909; Baldoni). Traces may continue for three days or longer. The feces do not contain it after twenty-four hours (Valdiguié and Lacaze, 1919). The maximum in the urine is reached in four to ten hours, independent of the dose or method of administration. This would indicate that doses should be repeated every three or four hours. The excretion is delayed in severe nephritis and diminished in cardiac decompensation (Porak, 1918).

ANTIMALARIAL DRUGS

Before the discovery of cinchona, the competing civilizations of the world were alike conquered and sometimes extinguished by malaria. The advent of quinine has completely changed the outlook, but the importance of malaria has continuously increased, with the increased crowding of the world, and the need of more intense colonization of the tropics. The disease is said to affect almost constantly 800 millions of people (Müller, quoted from Dawson), and to cause annually two million deaths (Ross; ibid.). The treatment of malaria was revolutionized by the discovery of quinine, but its use remained empirical, lighted only in part by discovery of the malarial organisms, the plasmodia, by Laveran, 1880. The mechanism of its action is still unknown. The vital importance of the malaria problem in the World Wars gave opportunities for more accurate study. New paths of approach were opened by the introduction, through Wagner von Jauregg, of intentional malaria inoculation as a treatment of syphilitic paresis, and by experimental malaria in animals. They led to synthetic antimalarial agents not closely related to quinine; especially to quinacrine, which is actually more effective than quinine. Intensive screening of over 14,000 chemicals during World War II produced several compounds of the 4-aminoquinoline series which appear superior to quinacrine (review R. L. Loeb *et al.*, 1946).

Clinical Success.—Adequate and safe dosage of quinine or of quinacrine produces prompt suppression, although rarely if ever complete eradication of the malaria. Within one to five days, usually three, if quinine is given by mouth, or within one or two days if given by vein, the plasmodia of benign tertian malaria disappear from the circulating blood and with them disappear the febrile paroxysms caused by the developmental cycle and the consequent destruction of the corpuscles. Failure to respond to these drugs, if they have been absorbed, is probably nonexistent, nor is there any acquired resistance or "fastness." The viscera, however, of most and possibly all treated patients continue to harbor some plasmodia which multiply at times to produce clinical attacks, "relapses," sometimes after many months, generally under conditions of strain or lowered general resistance, for an average of a year with falciparum infections, two years with vivax, ten years with quartan (J. Hayman, 1946). Relapses occur in a third to half of the vivax infections, much less frequently with the falciparum. Each relapse decreases the liability to further relapses.

Recurrences do not occur in persons inoculated with infected blood, nor in natural inoculation if there has been no therapy. Quinine and quinacrine appear to kill the trophozoites completely, the sporozoites only partly (M. F. Boyd, 1940, 1942). The surviving plasmodia have been greatly modified, especially as regards their rate of multiplication. In acute attacks this is such that the survival of 4 per cent of the parasites would suffice to reproduce the original number by the time of the next cycle. The "cure" checks this multiplication in two directions: A part of the plasmodia propagate into the sexual forms which cannot multiply until they have passed through the mosquito. These are, therefore, harmless to the patient, but render him an infective carrier. Another part of the plasmodia remain asexual, but their multiplication is not sufficiently vigorous to overwhelm the normal destructive mechanisms; at the same time, the sluggishness of these plasmodia appears to render them resistant to destruction by quinine as well as to the natural protective agencies, so that a rather stable balance is established. If this is temporarily upset, multiplication resumes, the patient is self-reinfected, and the typical ague attacks set in; and with this, the plasmodia recover their susceptibility to quinine treatment, although often not quite in the same degree, *i. e.*, chronic malaria is less amenable to quinine. This is not due to adaptation to the drug, for it also occurs if the earlier attacks were not treated. It is a common phenomenon of protozoan infections.

The tendency toward later relapses is less if the original treatment was early, intensive and prolonged for some time after the symptoms had been suppressed, as already noted by Sydenham. Excessive dosage, however, may do more harm than good to the patient; and prolonged treatment tends perhaps to hinder the development of the natural mechanisms which build up a lasting defense more effectively than does chemotherapy. The Malaria Commission of the League of Nations (Third and Fourth General Reports, 1933 and 1937) therefore recommends merely to treat the individual attacks, which generally become progressively milder until the disease is practically extinguished, rather than to prolong the chemotherapy beyond the symptoms, as was the usual practice. This policy applies also to quinacrine.

Susceptibility of Plasmodia Species and Their Developmental Cycles.—Quinine and quinacrine are nearly equally effective against the circulating trophozoites and other asexual forms of the vivax and quartan plasmodia, which are responsible for the febrile paroxysms. Adequate doses also destroy most of the sexual gametocytes of these species, which develop between the attacks and infect the mosquito (M. F. Boyd, 1944). Quinacrine is more effective than quinine against falciparum (malignant tertian). Neither drug precludes vivax relapses; pamaquine decreases recurrence materially if administered for ten days, not if confined to two days (Hayman). Totaquine (mixed cinchona alkaloids) is not suitable for falciparum. The *timing of the administration* with reference to the attack is practically immaterial (Maxcy, 1928). Pamaquine in safe doses has relatively little effect on the asexual forms and does not modify the clinical course, but it devitalizes the infecting stage of the falciparum, and renders most patients noninfectious (Boyd).

Visceral Foci.—When the plasmodia are introduced by a mosquito they disappear almost instantly from the circulating blood, lodge in the reticulo-endothelial system, and do not reappear in the circulation until several days, when they have multiplied to overflow. These exo-erythrocytic foci are also centers for late relapses and probably for sexual development. Antimalarial drugs do not reach these "visceral centers" in sufficient concentration to be effective. Injection of malarial blood does not at first involve the reticulo-endothelial system, and is, therefore, much more amenable to treatment. Falciparum owes its high mortality to the rapid multiplication of the parasites and rapid destruction of the blood cells. A sticky substance agglutinates them and obstructs the circulation, so that most of the plasmodia are in stagnant capillaries where drugs do not penetrate (E. C. Faust, 1945).

The mechanism of action of the antimalarial drugs has not been established; it is perhaps through interference with metabolic processes necessary to development and multiplication of the plasmodia, somewhat analogous to "antibiotic" agents (review, E. K. Marshall, 1944).

The multiplication of Plasmodium knowlesi is suppressed by the same concentration of quinine and of quinacrine *in vitro* as *in vivo*, indicating that these substances act without "intervention" of the body (E. G. Ball, 1946). The effect of quinine is not due to direct *lethal* action on the plasmodia, for *in vitro* this is not materially greater than with nonspecific drugs, and the concentrations of quinine required to kill the plasmodia are much higher than those which exist in the blood in quinine treatment. Nor has it been possible to demonstrate that quinine stimulates the production of specific or nonspecific antibodies; nor is the action due either to an antipyretic or to a colloidoclastic reaction, for other agents which produce these effects are not specific against malaria. Quinacrine, on the other hand, is directly fatal to the plasmodia.

Blood Concentration and Parasite Count.—If the action were directly parasiticidal, the number of plasmodia in the circulating blood should fall lowest when the concentration of the drug is highest. This is not so with *quinine*, according to observations on rhesus monkeys infected with Plasmodium knowlesi (R. N. Chopra, Ganguly and Roy, 1935). The highest concentration of *quinine* obtainable by intravenous injection without too severe toxic effects does not reduce the number of parasites or cause their degeneration until after some hours, when the concentration has already fallen; and a single dose of quinine, no matter how large, is effective if the number of parasites is low, less than 100,000 per cubic millimeter. If the treatment has been successful, nearly all the parasites disappear, and the few that remain multiply but slowly and feebly, although practically no quinine remains in the blood. The action therefore appears to be indirect. With quinacrine (Chopra *et al.*, 1936), the number of parasites begins to fall as soon as the concentration of the drug rises, so that there is probably a direct lethal action on the plasmodia, but the full effect is not reached for some twenty-four hours, so that there is probably also an indirect action. However, as further indication of direct action, a single dose of quinacrine is effective even if the parasite count is high, above 500,000 per cubic millimeter; and the remaining parasites, when they reappear in the peripheral blood, multiply at the same rate as in the original attack, and result in death.

The *experimental inoculation of malarial blood* in the treatment of paresis, introduced by Wagner von Jauregg, 1918, offered an immediate test for direct antiplasmodial action. In this treatment, the patient receives a subcutaneous or intravenous injection of 5 cc. of the blood of a patient with benignant tertian, removed at the height of the paroxysm. After a latent period of above five days, this induces typical malaria, which may be arrested at any time by relatively small doses of quinine. Kirschbaum, 1923, found that incubation of the malarial blood for twenty-four hours, with an equal volume of quinine hydrochloride, 1: 5000, in isotonic saline or dextrose, does not destroy its virulence, although this quinine concentration is at least ten times greater than the clinical peak concentration. On the other hand, incubation with neoarsphenamine for three to six hours destroys the virulence. It has been objected that these conditions are not physiological (Giemsa, 1927), but this renders the resistance to quinine only more remarkable, and speaks strongly against direct plasmodicidal action. The experiments were confirmed by Yorke and MacFie (Maxcy, 1931), and extended by S. P. James *et al.*, 1927, to the sporozoites of the mosquito: infection followed the injection of blood serum containing quinine, 1: 5000, in which infected anopheles had been teased and left in contact for fifteen minutes. Evidently, concentrations of quinine much higher than can exist in the blood do not kill the plasmodia directly. Administration of quinine to malaria-infected canaries interferes with the normal growth and development of the parasites (E. M. Lourie, 1934). *Quinacrine* is directly plasmodicidal, so that blood of monkeys heavily infected with Plasmodium knowlesi loses its virulence when digested twenty-four hours with an equal volume of quinacrine solution, 1: 25,000 (Chopra *et al.*, 1936). The atabrine becomes firmly bound by the parasites (F. M. Peter, 1935).

Direct Injury of Plasmodia by Quinine under Extreme Conditions.—Laveran, 1880, the discoverer of the plasmodia, observed that their *motility on a slide* is arrested by quinine, 1:1000. However, this concentration is a hundred times greater than occurs clinically. Many substances not antimalarial are fatal to plasmodia in lower concentrations.

Many observers, for instance, Lo Monaco and Panichi, 1899, observed *degenerative changes in the plasmodia* of quinine-treated patients. This shows that the parasites have been injured, but not whether by direct action. Bass, 1922, found that incubation of *cultures of plasmodial blood* with quinine, 1: 9000, for five hours appeared to check the development and alter the stainability of the plasmodia as compared with controls, but the objection of abnormal concentrations holds against these observations, as against those of Laveran; and as with these, similar effects are produced by many substances which are not antimalarial. It has also been suggested that the parasites are killed by a decomposition product of quinine; but all the known decomposition products are much less effective than quinine. Giemsa, 1927, reviewing the theories, inclines to a direct plasmodicidal action in the *capillaries*, where quinine is adsorbed and concentrated on the endothelium. It was suggested that the surface affinity of quinine may cause its *adsorption* on the surface of the corpuscles (Morgenroth, 1918; O. S. Gibbs, 1928), to form a resistant film which would hinder the penetration of the merozoites, and so prevent the completion of the cycle; this is not supported by direct evidence. *Blocking of the reticulo-endothelial system* with trypan blue decreases the effectiveness of quinine, pamaquine and quinacrine in avian malaria (Kritschewski and Demidowa, 1935).

The *blood picture and the spleen are not affected in normal individuals* by antimalarial doses of *quinine*, by mouth or by vein. Patients with chronic malarial splenomegaly who respond favorably to quinine, react with transient leukocytosis, especially of the large lymphocytes and monocytes, with coincident reduction in the size of the spleen and increase of erythrocytes (with intravenous injection, the red count may be temporarily diminished by hemolysis). These changes are absent if the quinine is not successful against the infection, indicating that there may be a causal relation. Pamaquine causes a temporary increase of lymphocytes, but a sharp fall of the monocytes, and does not contract the spleen (Hughes and Shrivastava, 1930).

Toxicity for Paramecia.—Before the discovery of plasmodia, C. Binz, 1868, surmised that malaria was due to protozoan parasites, which could be killed by quinine, since he found that this is highly toxic to infusoria *in vitro*. Paramecia have been widely used as a presumptive index of antimalarial action (C. Binz, 1869; G. Grethe, 1896), but no definite relation has been established; in fact, substances with a paramecia toxicity as high as quinine are totally devoid of antimalarial action (U. N. Brahmachari *et al.*, 1930). Incidentally, dilute solutions of quinine, or brief contact with concentrated solutions, stimulate the multiplication of paramecia. The toxicity is materially greater in light than in the dark (M. Feiler, 1928). Continued exposure to low concentrations increases the resistance to quinine; the susceptibility is restored by small doses of sodium arsenite, which have no apparent effect when used alone (Neuschloss). Pamaquine, strychnine, aconitine and solanine, like quinine, stimulate growth and division in low concentrations (10^{-12} to 10^{-21}), and depress in somewhat higher concentrations (10^{-12} to 10^{-5}). Keeping the cultures in the dark greatly decreases the toxicity of solanine as well as of quinine, but has no effect on the pamaquine and the other drugs (Feiler, 1928, 1929). Colpidium cultures tolerate a maximum concentration of 1:2000 acutely, but if adapted by *gradually increasing amounts*, tolerance to a concentration of 1:300 is established (O. Harnisch, 1926).

Amebic Dysentery.—Quinine is used by rectal irrigation. Its administration by mouth (2 Gm. per day) is sometimes effective, but less certain than emetine (Brooks. 1914). Slow rectal injection of 1 or 2 liters of 1:2000 to 1:1000 solution has been advocated for local action (W. Fletcher, 1924).

Treatment of Malarial Paroxysms.—Quinacrine and quinine are both fully effective in suppressing and treating the clinical attacks of benign tertian and quartan malaria. The febrile attacks are suppressed within thirty-six hours, and the trophozoites disappear from the blood, generally by the third day. Quinine reaches effective plasma concentrations sooner than quinacrine, which is partly fixed in the tissues; but this can be practically compensated by higher initial dosage (Findlay and Stevenson, 1944). Quinacrine is probably the less toxic drug under these conditions, but both drugs are subject to toxic side actions, which may enforce the choice. The preferred routine during the war consisted of 0.2 Gm. of quinacrine hydrochloride with 1 Gm. of sodium bicarbonate and a tumbler of water every six hours for five doses, followed by a 0.1 Gm. tablet three times daily after meals for six days. If quinacrine is not tolerated, *quinine* or *totaquine* is given, 1 Gm. three times daily before meals for two days, followed by 0.6 Gm. three times daily for five days (J.A.M.A., 1945, *128*:1101; M. F. Boyd, 1944).

Intramuscular injection of quinacrine may be used if vomiting interferes with oral administration; 0.2 Gm. in 5 or 10 cc. of water into each buttock (total, 0.4 Gm.). Two additional injections of 0.2 Gm. may be given six to eight hours apart, changing to the oral administration as soon as the drug is retained.

Intravenous administration of quinine is indicated if the patient is in *coma*, or if the blood film shows high population of falciparum; injecting *very slowly* (in not less than thirty minutes) 0.6 Gm. of quinine hydrochloride in 300 cc. of normal saline. Hanzlik and Cutting, 1945, recommend addition of 1 mg. of epinephrine. This may be repeated in six to eight hours if necessary; or, preferably, an intramuscular injection of quinacrine may be given immediately after the quinine.

Pamaquine naphthoate, 90 mg. with 2 Gm. of quinine daily for ten to fourteen days greatly decreases the incidence of relapse in vivax malaria. The two drugs together apparently accomplish the eradication of the plasmodia when neither is effective alone (D. R. Talbot, 1943; R. W. Berliner *et al.*, 1946). A smaller dosage, 10 mg. three times daily after meals, has been administered during the last five days of the ordinary quinine treatment or begun two days after quinacrine was stopped, and continued for five days, to prevent spread to mosquitoes It should be stopped if untoward symptoms develop. This dosage is toxic to the gametocytes, but not to the asexual forms, and therefore has no effect on the attack. It should not be administered at the same time as quinacrine, as their toxicity is additive.

Therapeutic malaria induced in paresis by the injection of blood from patients carrying a vivax strain, or by mosquitoes infected from such patients, is peculiarly amenable to quinine, so that the administration need not be continued beyond three dyas (Yorke and MacFie, 1924). *Oxophenarsine hydrochloride* (*Mapharsen*) is effective against therapeutic malaria. A single intravenous injection of the antisyphilitic dosage generally terminates the paroxysms, but three or four injections are given to obviate recurrence (D. Goldman, 1938). Tertian malaria resistant to quinine alone may respond promptly to one injection of 40 mg. of oxophenarsine hydrochloride. It is advisable, however, to follow this with four injections of 40 mg. at weekly intervals (W. H. Stewart, 1945). Intensive bismuth therapy, especially with thioglycollate, checks therapeutic malaria, but does not eradicate it (W. F. Schwartz, 1939). *Sulfanilamide* is somewhat effective against mild malaria attacks (J. H. Williams, 1941); as is also *methylene blue.*

Screening of antimalarial agents utilizes the malarias of birds and apes. The results cannot be transferred directly to man, as the efficiency for different plasmodian species is not necessarily parallel. Several species of parasites should be used. The comparative potency is expressed as multiples of the effective dose of quinine or quinacrine or other established drug (review, E. K. Marshall, 1942; 1946). Bird malaria especially has been used to study the relation of chemical constitution to action (Giemsa *et al.*, 1926; Hegner *et al.*, 1930; *Quinacrine*, P. Tate and Vincent, 1934; *Pamaquine*, Hegner and Manwell, 1927; Lacorte, 1927).

Quinoline compounds with diethyl-amino alkaline chains in the 8 position are both schizotropic and gametotropic; those in the 4 position are only schizotropic (Galperin).

Relapses should be treated as they arise, generally less energetically than the original attack. They become progressively milder by the development of natural defense mechanisms.

Relapses may be provoked by stress and strain and overfatigue. Plasmodia may sometimes be mobilized by epinephrine, 0.5 cc. of 1:1000 hypodermically. This defers, but does not prevent, recurrence and is not recommended.

"*Blackwater fever*," attacks of serious *hematuria* following on spontaneous intravascular hemolysis, may occur during quinine treatment of a relapse of falciparum malaria, after repeated previous attacks treated with quinine without hematuria. It also occurs with quinidine and cinchonine (Leverani, 1929), and with pamaquine (Earle *et al.*, 1946), but rarely, if ever, with quinacrine.

Quinine hemolysis evidently involves sensitization. Quinine is not hemolytic for normal blood. The affected erythrocytes hemolyze when transferred into a normal individual, and normal red cells injected into a sensitized individual hemolyze as quickly as the patient's red cells (H. Foy *et al.*, 1945). It is interpreted as involving two factors: (1) increased fragility of the erythrocytes to lysolecithin; and (2) a circulating hemolysin (H. Most and Meleney, 1944). The parasitized cells develop greater mechanical fragility (S. C. Shen *et al.*, 1946). C. McGuire, 1945, suggests that the liver is involved in the sensitization, as many subjects have amebic liver injury

Suppressive Treatment.—Vivax malarial attacks do not develop while appropriate doses of quinine or quinacrine are taken. They do not prevent the infection, but the parasites do not multiply in the visceral foci sufficiently to produce clinical symptoms. If the medication is suspended at any time, multiplication resumes and progresses, and a "delayed primary attack," often more or less atypical, develops in several weeks or months, most frequently between the third and ninth week (I. M. London *et al.*, 1946). It can be controlled by quinacrine, 1 Gm. in divided doses on the first day, followed by 0.3 Gm. daily for six days (H. Most and Hayman, 1946). The deferment may be convenient temporarily, and does no harm, but the vivax infection will rarely be cured until the attack is permitted to develop. Falciparum infection is suppressed indefinitely after medication is discontinued (O. R. McCoy, 1945; M. F. Boyd, 1944).

Quinacrine appears to be more effective than quinine and is generally better tolerated. Nausea generally disappears when its use is continued. The maintenance dosage is a tablet of 0.1 Gm. daily, at the evening meal. This dosage requires two or three weeks to establish a full plasma concentration; it is, therefore, advisable to begin the administration one to four weeks before the expected exposure. If quinacrine is not tolerated, *quinine sulfate*, 0.5 to 0.65 Gm., may be taken daily at the evening meal. Cinchonism from this dosage is not serious with most people, and decreases with use. There is no evidence of the production of drug-resistant strains (A. Missiroli, 1939).

Drug eradication of malaria from a locality by curative or prophylactic treatment is practically impossible with the present drugs; but systematic periodic blood examination and treatment with quinacrine or quinine, followed by pamaquine, materially lowers the incidence (Gorgas Memorial Laboratory Annual Report, 1941).

Experimental infection of syphilitic patients with vivax and falciparum sporozoites is prevented by administering 160 mg. of pamaquine naphthoate on the day preceding and for five or six days after the inoculation. Smaller doses and shorter periods are ineffective (H. A. Feldman *et al.*, 1946).

Oral administration of quinine is to be preferred; absorption is sufficiently prompt so that the saving of time by parenteral injection is not significant. The next paroxysm is likely to occur in any case; but the attacks should be suppressed by the third or fourth day with quinine, by the sixth or seventh with atabrine. Quinine should be given before meals. Experiments with bird malaria indicate that divided doses are more effective and less toxic than the same amount in a single dose (Sergent and Sergent, 1921; H. Beckman, 1944). The absorption is more prompt if the quinine is given in solution, the sulfate being dissolved with a slight excess of dilute sulfuric acid to prevent precipitation in the mouth by the alkalinity of the saliva. Tablets or capsules of quinine sulfate (not more than 0.3 Gm., 5 grains each) practically avoid the bitterness and are adequate, except perhaps on the first day. Old pills made with ordinary excipients may give but little absorption. For children, the dosage may be reduced in proportion to body weight, and the sulfate may be suspended in syrup of chocolate or of yerba santa. The tasteless quinine esters (euquinine and aristoquine) require hydrolysis by the acid of the digestive tract and are, therefore, less effective than the soluble salts of quinine, especially in hypochlorhydria (Biginelli, 1928). Cinchona preparations are less effective than quinine salts, and adequate doses contain so much tannic acid that they may upset the digestion. *Totaquine* is considerably cheaper than the purified quinine (P. F. Russel, 1935). *In case of idiosyncrasy*, quinidine or cinchonine may be tried.

Parenteral administration should be used only when the oral is impossible, in coma, vomiting, or high pyrexia. In such case intramuscular quinacrine should be preferred, since quinine is irritant and poorly absorbed from intramuscular injection and may cause sudden death when administered intravenously.

Intravenous injection (introduced by G. Baccelli, 1890) initiates the action more promptly, especially in moribund patients. Its final effectiveness is no greater, however, since the concentration in the blood drops in a few moments to the same level as with oral administration (S. Weiss and Hatcher, 1929; Chopra *et al.*, 1934). On the other hand, the intravenous injection produces exaggerated cinchonism and involves serious risk of acute and sometimes fatal circulatory collapse, as also local irritation. In view of these objections, it should be used only in moribund patients with algid collapse. A single intravenous dose of 1 to 2 Gm. of quinine and urea hydrochloride in 10 cc. of water, injected *very slowly* may clear conditions sufficiently to continue with oral administration. Quinine dihydrochloride presents more danger of flocculation, but has been used, 10 grains (0.65 Gm.) in 100 cc. of normal saline injected by gravity, or in 20 cc. by syringe, with great caution, stopping the injection (at least temporarily) if collapse develops. In emergencies, ampuls containing the above dose in 20 cc. of saline may be used, with a syringe, but with even greater caution and slowness. Care must be taken that the solution does not infiltrate the walls of the vein or the subcutaneous tissue, else sloughing or fibrosis may result (L. S. Dudgeon, 1919). Idiosyncrasy is generally a definite contraindication. Circulatory embarrassment enjoins extra caution; so also does the recent use of large doses of quinine.

Acute Side Actions of Intravenous Quinine Injections.—More or less cinchonism is the rule, setting in during the injection, with bitter taste, ringing in the ears, blurred vision, mental confusion and vertigo. These increase with the rapidity of the injection, but are usually not dangerous. They attain their maximum in three to ten minutes, then gradually subside for several hours. The blood pressure falls acutely, clinically as well as in animals, especially with rapid injections of concentrated solutions (Brahmachari, 1922; R. McCarrison and Cornwall, 1919). Concentrations of 1:150 are dangerous (MacGilchrist); immediate death has been reported (see Eggleston, 1917). On the other hand, even 10 per cent solutions have been injected without serious effects (A. D. McLean, 1917). More or less fall of pressure is probably present in all cases, but it is usually of short duration. The degree and duration depend partly on the speed of injection, partly on the patient. The mechanism is by cardiac depression, and probably also by colloid flocculation. The onset of collapse is indicated by profuse sweating, dilation of the pupils, staring expression and twitching of the facial muscles. Epinephrine is used as antidote.

Intramuscular injections (quinine dihydrochloride, 1 Gm. in 10 cc.; or quinine-urea hydrochloride, 2 Gm. in 5 to 10 cc.) are not absorbed more rapidly than the oral doses, and they cause considerable local irritation, especially if they are made too near to the sciatic nerve (Sicard *et al.*, 1917).

Rectal injections of quinine give but little absorption, and solutions of ½ to 1 per cent are so irritating that they are not retained over twenty minutes, and are followed by inflammation. Colonic irrigation with 1 or 2 liters of 1:2000–1000 solution of quinine sulfate or hydrochloride may be used in *amebiasis.*

Antimalarial Action of Other Cinchona Alkaloids and Quinine Derivatives.—The clinical evidence, reviewed by Dawson, 1930, indicates that the common cinchona alkaloids, quinine, quinidine, cinchonine and cinchonidine, are practically equivalent in equal dosage, nor is one seriously more toxic than the others. The greater experience with quinine, however, should cause this to be preferred, except in idiosyncrasy, when quinidine or cinchonine may be substituted. Of these, quinidine comes nearest to quinine (Sanders and Dawson, 1932), and it may be even more effective in malignant malaria. Its systemic toxicity is about a third higher. It is administered as the sulfate, 0.65 Gm., 10 grains daily.

The *plasma concentration,* milligram per liter, required to suppress blood-induced vivax malaria is: quinine, 5; quinidine, 0.9; cinchonidine, 2; cinchonine, less than 0.1. The effective oral dosage, however, does not show much difference (Zubrod *et al.*, 1946).

Cinchonine and **cinchonidine** produce clonic and tonic convulsions, located below the optic thalami. They are more depressant to the heart than is quinine (Albertoni, 1882). Their cardiac actions were studied by Chopra *et al.*, 1928, and various pharmacological actions of cinchonidine by Provinciali, 1932 and 1938. They are similar to quinine.

Quinamine differs quantitatively from quinine. It is less toxic for bacteria and protozoa, markedly more tonic for the uterus, and is a more potent local anesthetic (Chopra and David, 1927).

Cinchonamine.—This is more toxic than quinine (F.D., 75 mg. per Kg. of dogs or cats). It produces salivation, hallucinations and epileptoid cerebral convulsions. It has little effect on blood pressure (Ellrain).

Totaquine, the mixed alkaloids of cinchona bark, is clinically practically as potent as the same dose of quinine (National Research Council, 1944; J.A.M.A., *125*:977).

Quinicine and Cinchonicine.—When quinine or cinchonine is heated with acid, the linking CHOH is hydrolyzed to CO, the two H's being transferred to the adjacent C and N of the loipon, forming an imide group and breaking the benzol ring. These compounds were discovered by Pasteur in 1853 and named by him quinicine and cinchonicine. Chemists, impressed by exaggerated estimates of the toxicity of quinicine, suggested that the toxic actions of quinine are due to the formation of quinicine by the gastric acidity, and that this formation in mixtures of quinine with organic acids would constitute a dangerous incompatibility. These fears are quite unfounded, both because quinicine (quinotoxine) is not much more toxic than quinine itself, and because only insignificant traces of it can be formed at ordinary temperatures even with organic acids, and still less with mineral acids (Biddle, 1912; Ad. Kaufmann). Incidentally, the formation of these compounds is indicated by black discoloration.

There need be no fear of prescribing solutions of quinine and dilute mineral acids, although organic acids should be avoided. Discolored and precipitated solutions should not be used, since they would be deficient in the therapeutic qualities of quinine.

The yellow or green *discoloration of quinine solutions* on aging or sterilization is produced by oxidation products, catalyzed by the presence of traces of copper (Bachstetz and Cavallino, 1934). The change would scarcely be sufficient to affect the actions.

Miller and Rhode, 1895, proposed to change the names to *quinotoxine* and *cinchotoxine*. The change has been largely adopted, but seems confusing and unjustified. The toxicity is not very high; and practically the same name, *quinatoxine*, had previously been applied by Ostermayer, 1884, to a quite different substance, diquinoline dimethylsulfate. This produces curare actions (Hoppe-Seyler, 1880; Durdufi, 1889).

Actions of Quinicine (Quinotoxine).—Bachstetz and de Caro, 1932, reported that the MLD for rats is a fourth that of quinine; for mice, one-half. Hildebrandt claimed that it is not convulsive, that it has a digitoxin effect on the frog heart, and that it raises the blood pressure slightly. Biberfeld found the toxicity for mammals low (lethal dose, 15 mg. per Kg. by vein; 200 mg. hypodermically, corresponding to about ½ ounce in man). In this large dose it produced convulsions. It did not have a digitoxin effect on the exposed frog heart, but depressed it like quinine. It also depressed other smooth muscle, produced local anesthesia similarly to quinine, but was not antipyretic.

Actions of Cinchonicine (Cinchotoxine).—The toxicity of this is also low. Hildebrandt found the hypodermic lethal dose as 150 mg. per Kg. for mice (equivalent to 10 Gm. for a man). The same dose of cinchonine was not toxic. Hunt obtained about the same number for cinchotoxine (310 mg.) as for quinine (370 mg.). Rabbits seem considerably more susceptible (Biberfeld, M.F.D. hypodermic, 10 mg. per Kg.; Fraenkel, F.D. hypodermic, 30 mg. per Kg.; Hildebrandt, cat, F.D. hypodermic, 20 mg. per Kg.). Death is preceded by violent convulsions. Hildebrandt described a slight rise of blood pressure. Biberfeld found depression of the circulation. Fraenkel observed on the exposed heart, first strong contractions, then diastolic arrest.

Ultraviolet Radiation on Toxicity of Quinine and Quinidine.—Macht and Teagarden, 1923, reported that these alkaloids are more toxic to rats exposed to the sunlight or to the quartz lamp, than to those kept in the dark. Quinine was more toxic than quinidine. The radiation, without quinine, had only a slightly stimulant effect on the muscular activity. *Exposure of quinine solutions to ultraviolet rays* apparently produces chemical changes by which it is rendered more toxic to paramecia *in vitro*, and also more effective against canary malaria (G. Roskin and Romanowa, 1929).

PREPARATIONS.—The ordinary salts of quinine are white, odorless and intensely bitter. They are *incompatible* with alkalis and other alkaloidal precipitants, and with salicylates, benzoates and tartrates (*not* with iron salts). Solutions containing free organic acids deteriorate slowly. *Average dose of all quinine salts:* 1 Gm., 15 grains, daily; individual doses vary from 0.06 to 0.6 Gm., 1 to 10 grains.

Quinine and Urea Hydrochloride, a double salt of quinine hydrochloride and urea hydrochloride, corresponding to about 62 per cent of anhydrous quinine. Freely soluble in water (1 Gm. in 1 cc.) with strongly acid reaction. *Quinine and Urethane Injection*, U.S.P., in water for injection, approximately 2 parts of quinine hydrochloride to one part of urethane. Usual size, 0.25 Gm. of quinine hydrochloride and 0.125 Gm. of urethane in 2 cc. *Quinine Bisulfate*, U.S.P., $Qu.H_2SO_4.7H_2O$, freely soluble in water (1 Gm. in 10 cc.) with strongly acid reaction. *Quinine Dihydrochloride*, U.S.P., Qu.2HCl. Freely soluble in water (1 Gm. in 0.6 cc.) with strongly acid reaction. *Quinine Ethylcarbonate* (*Euquinine*); fleecy crystals, only slightly soluble in water and practically tasteless. **Quinine Hydrochloride**, U.S.P., $Qu.HCl.2H_2O$. Soluble in water (1 Gm. in 16 cc.) with neutral reaction. Average dose, oral, 0.6 Gm., 10 grains; intramuscular, 0.2 Gm. **Quinine Sulfate**, U.S.P., $Qu._2H_2SO_4.2H_2O$. Fleecy white crystals, acquiring brown tint when exposed to light. Very bitter. Sparingly soluble in water (1 Gm. in 810 cc.), with neutral reaction. *Quinine Sulfate Tablets*, U.S.P., usually contain 0.12, 0.2 and 0.3 Gm. (2, 3 and 5 grs.). *Tinctura Antiperiodica* (Warburg's Tincture) contains 1.5 per cent of quinine hydrochloride, 0.3 Gm. per tablespoonful, with rhubarb, aloes and aromatics. Used in India against malaria. *Cinchonine Sulfate*, $(C_{19}H_{22}N_2O)_2H_2SO_4.2H_2O$; differs from quinine in being dextrorotatory and can sometimes be used successfully in persons who have an idiosyncrasy to quinine; white, lustrous crystals; soluble in water (1:60). Dose, 0.15 Gm., 2½ grains. *Totaquine*, U.S.P., a mixture of alkaloids from the bark of Cinchona species, containing not less than 10 per cent of anhydrous quinine, and about 75 per cent of total cinchona alkaloids. Yellowish to pale brown powder. Almost insoluble in water. Average dose, 0.6 Gm., 10 grains. *Totaquine Capsules*, U.S.P., and *Totaquine Tablets*, U.S.P.; usual sizes, 0.12, 0.2 and 0.3 Gm. *Cinchona*, N.F. (Peruvian Bark), the dried bark of various species and hybrids of Cinchona, known in commerce as Red or Yellow Cinchona, which yields not less than 5 per cent of Cinchona alkaloids (6 per cent, of which not less than one-half is quinine and cinchonidine, B.P.). Dose, 1 Gm. (0.6 to 4 Gm.), 15 grains (10 grains to 1 drachm). *Comp. Tincture of Cinchona*, N.F., 10 per cent of cinchona flavored with serpentaria and bitter orange peel. The B. P. is colored red with cochineal. Dose, 4 cc., 1 drachm.

QUINACRINE

Quinacrine (*atabrine, atebrin, mepacrine*), invented by Mauss and Mietzsch, 1933, is an alkyl-amino-acridine derivative with the same side chain as pamaquine. Its antimalarial use was discussed in the preceding section. Like quinine, it acts chiefly on the trophozoites. Its *efficiency* both against vivax and falciparum malaria is generally superior to that of quinine, both for suppression and for clinical treatment. Widespread clinical attacks of falciparum were practically eliminated by its use in the U. S. Army, and deaths from malaria have become extremely rare (C. S. Livingood and Dieuaide, 1945). The therapeutic dosage is usually well tolerated. The *skin* is colored yellow, starting in about a week and persisting for two or three weeks after administration is discontinued. The color is due to the drug, not to bile. The action by mouth occurs so promptly that parenteral administration is rarely necessary. If vomiting prevents oral administration, the doses may be injected by rectum or intramuscularly. Intravenous injection should be avoided, as it involves more risk, especially in view of the slow excretion.

Quinacrine is also effective against *giardiasis*. Administer 0.1 Gm. (1½ grains) by mouth three times daily for five days; then an interval of five days before it is repeated (Morrison and Swalm, 1939). Promising results have been reported in *spotted typhus* (P. van Meerendonk, 1942).

Fate.—Quinacrine is quickly *absorbed* from the intestines, but its *plasma concentration* rises slowly. It is *excreted* by the urine and somewhat by the bile. The urinary excretion starts within fifteen to sixty minutes, but proceeds slowly, a considerable part being retained in the tissues, including the skin.

With the clinical dosage continued for forty-five consecutive days, the *excretion by the urine*, which becomes intensely yellow by the third to fifth day, gradually increases to 6–11 per cent of the daily dose. After the last dose the excretion declines; in fifty-five days it is less than 1 per cent of the original dosage (F. E. Kelsey *et al.*, 1944). Part of the excreted drug is unchanged, part exists as acridine derivatives, varying in different animal species (Scudi and Jelinek, 1944).

The *plasma concentration* of quinacrine rises gradually from the beginning of the treatment and falls slowly on ending. Repeated doses eventually attain an equilibrium (never more than 1 mg. per 100 cc.; Scudi and Hamlin, 1943), about the end of the fourth week, and then continues practically constant as long as the dosage is maintained (J. A. Shannon *et al.*, 1944). A week of constant dosage reaches about half of the eventual level. The equilibrium level can be attained in two weeks if the dosage is doubled in the first week. On discontinuing administration of ordinary doses, the level falls to half in two weeks. Moderate doses of sodium bicarbonate or of alcohol do not affect the quinacrine level (P. K. Smith, Gallup and Cain, 1946).

The *tissue concentration* (fluoroscopic method; L. C. Craig, 1943; J. M. Mason, 1943) is highest in the liver, intermediate in the spleen, kidneys and bone marrow (Scudi and Hamlin, 1943; J. W. Jailer, 1945). It is also found in the brain (Fernando and Wijerama, 1935), and passes into the fetus (F. K. Oldham and Kelsey, 1945). In the liver it is diffusely distributed through the parenchyma, not especially in the Küpffer cells (Jailer, 1945). The amount in the liver may reach 6 per cent of the total dosage; nearly 5 per cent may be recovered from the bile (Annegers *et al.*, 1943).

A characteristic brilliant yellow fluorescence of the finger and toe nails, when illuminated by the Wood light, develops when quinacrine has been taken for a considerable time, as in prolonged suppressive routine. It begins to disappear in three to six months after discontinuing, but some may remain up to a year. The skin, hair and teeth do not have the fluorescence (Ginsberg and Shallenberger, 1946; Kierland *et al.*, 1946).

Toxic effects are not often a serious factor in oral administration of quinacrine, being less than with quinine; that of American manufacture is no more toxic than the original product (O. W. Barlow *et al.*, 1945). It does not produce auditory or visual disturbances; even prolonged administration does not diminish activity of vision in air pilots, except in rare instances (E. A. Abbey and Lawrence, 1946). Nor does its use for ten months produce significant changes in the liver and kidney function or in the blood (B. G. Macgraith, 1945). It does not affect the uterus, so that it may be used safely in pregnancy (N. Sapeika, 1934). The yellow color of the skin should not be a serious drawback. Its intensity is an individual peculiarity, not related to the duration of the administration (E. A. Abbey and Lawrence, 1946).

The most common side effects are dizziness, headache and rather mild *gastro-intestinal disturbances*, nausea, vomiting, sometimes diarrhea, starting several hours after administration.

They occur in a considerable proportion of subjects, especially with suppressive treatment, but decreased materially when the dosage was reduced from 0.2 to 0.1 Gm. (P. H. Long, 1946). They often disappear in a few days if the drug is continued and may generally be prevented by dilution and sodium bicarbonate.

Mild excitement occurs occasionally. More severe psychoses appear exceptionally toward the end of a week of energetic oral, not with suppressive, treatment (J. W. Field, 1943; Sheppeck and Wexberg, 1946); or after intramuscular injection (P. Wilkinson, 1944): erethismus, volubility, confusion, occasionally mania. They return to normal in about a week without treatment.

Hepatitis and other serious complications are rare even when suppressive treatment is continued for a year.

A few patients develop *chronic dermatoses*, lichenoid or eczematous, which may progress to exfoliative. They are more common with larger doses, and yield rather slowly on withdrawing the treatment. A few deaths from exfoliative dermatitis and hepatitis have been reported (C. M. Agress, 1946).

Edema of the corneal epithelium has been reported (F. M. Reese, 1946). It disappeared in three weeks after withdrawal, without permanent damage.

Livingood and Dieuaide, 1945, urge that the routine dosage should not exceed 0.7 Gm. weekly for suppression, or 2.8 Gm. in seven days for treatment; and that administration should be discontinued on the appearance of atypical lichen planus, unexplained chronic eczematoid dermatoses, exfoliative dermatitis, severe leukopenia, agranulocytosis and aplastic anemia, acute hepatitis or toxic pyschoses reasonably attributable to the drug.

Hypodermic or intramuscular injections of quinacrine hydrochloride are irritant and may produce necrosis (F. Hawkins, 1944). *Intravenous injection* of quinacrine is not justified. It may produce accelerated or slowed (gasping) respiration, circulatory collapse and death; or vomiting, fever and psychoses.

Industrial exposure to quinacrine dust gives a high incidence of irritation of the exposed mucous membranes, and especially of dermatoses of varying severity. Local deposition of the dye in the cornea may interfere with vision, but this clears after withdrawal from exposure (O. W. Barlow, Gorham and Bedell, 1946).

The acute toxicity of quinacrine for animals is rather low, and the effects not characteristic. It is a local irritant. Large doses produce gastro-intestinal irritation and cerebral stimulation. Rats show delayed passage of food through stomach and intestines, with gastric hypersecretion and hypertonus (Oxford Malaria Research Unit, 1944). Intravenous injection causes transient fall of blood pressure. It protects the heart against chloroform-epinephrine ventricular fibrillation (K. I. Melville, 1946). Perfusion of 1 to 1.5 mg. per liter through dog heart-lung preparations impairs the contractility of the heart muscle, increases venous pressure and diminishes cardiac output (L. H Smith and Stoeckle, 1946). There is little direct effect on the autonomic organs. The excretion is slow and imperfect as in man (G. Hecht, 1933; De Langen and Storm, 1934).

Continued administration to rats over extended periods produced no perceptible effect on weight or othersiwe with 25 mg. per Kg. daily; 40 to 65 mg. retarded growth (Hegsted *et al.*, 1944). Large oral doses (800 ppm in the diet) cause generalized yellow discoloration; large necrotic foci in the liver, with regenerative changes in the remaining liver tissue; fibrosis and focal necrosis in the cardiac and skeletal muscle; hyperplasia of bone marrow and leukocytosis; marked changes in the adrenal cortex, reticulo-endothelial system and kidneys, death by myocardial fibrosis and liver injury. The toxicity is increased by fasting, diminished by high protein and low fat diet (O. G. Fitzhugh *et al.*, 1945; H. Siegel and Mushett, 1944; Scudi *et al.*, 1944).

***Quinacrine Hydrochloride**, U.S.P.; *Atabrine di-Hydrochloride, Mepacrine Hydrochloride*, B.P.: a yellowish crystalline powder, of bitter taste. Soluble in water (1 Gm. in about 35 cc.), with acid reaction. Average dose, 0.1 Gm., 1½ grains. *Quinacrine Hydrochlordie Tablets*, U.S.P.; usual sizes, 50 and 100 mg., ¾ and 1½ grains.

CHLOROQUINE

Chloroquine, N.N.R., "SN7618," is the most promising of several 4-amino quinoline series drugs that appear superior to quinacrine and quinine in effectiveness against the erthrocytic forms of vivax and falciparum plasmodia. Its potency is about three times that of quinacrine. A single dose per week secures suppression. Acute attacks are terminated in one or at most two days, and falciparum is cured. With vivax it lengthens the interval between treatment and relapses considerably more than does quinine or quinacrine. It does not prevent infection. It is well tolerated, does not produce cinchonism, gastro-intestinal derangement and does not discolor the skin or cause serious dermatites. Its absorption, cumulation and fate resemble those of quinacrine (synoptic report, R. F. Loeb, Clark *et al.*, 1946).

Fate.—Chloroquine, 7 - chloro - 4 - (4 - diethylamino-1-methylbutylamino) quinoline, is practically completely *absorbed* from oral administration. The *urinary excretion* is slow, but rather more rapid than that of quinacrine. The *blood concentration* is somewhat higher than with quinacrine of the same dosage. Considerable amounts are *deposited in the tissues*, proportional to the dose, and distributed similarly to quinacrine. It is concentrated in the nucleated cells, especially in the liver, spleen, kidneys, lungs, and leukocytes to 200 or 300 times its plasma concentration; very little in nervous tissue. The greater part is *destroyed* in the body, as is quinacrine, only 10 to 20 per cent being recovered from the urine; the urinary output is increased by acidification and decreased by alkalinization of the urine. When administration is discontinued, it disappears slowly, the concentration in body fluids falling by about a third in a week.

The toxicity for experimental animals is about the same as with quinacrine, by oral administration, acutely or continued. The intravenous toxicity is somewhat higher for chloroquine.

Clinical side effects in the treatment of acute attacks are mild and transient headache, visual disturbances, pruritus, gastro-intestinal symptoms. Continued use of 0.5 Gm. weekly for eleven months does not produce any serious symptoms or impair general health.

The *dosage* for suppression is 0.3 Gm. once each week. For acute attacks, Most, London *et al.*, 1946, recommend one tablet of 0.3 Gm. when the diagnosis is established by blood smear, repeating this in four hours and on each of the following three mornings, making a total of five tablets (1.5 Gm.) during four days.

It is marketed as **Chloroquine Diphosphate** (*Aralen diphosphate*).

PAMAQUINE NAPHTHOATE (PLASMOQUINE, PLASMOCHIN, AMINOQUIN)

This butylamino quinoline derivative is somewhat effective against the erythrocytic forms of vivax and falciparum plasmodia, but its potency against these is limited, even with maximum tolerated dosage (J. V. Taggart *et al.*, 1946). It acts chiefly on the gametocytes and may be used when these continue in the blood after quinine or quinacrine, to diminish the liability to relapse and to render the patients noninfective to mosquitoes. The administration was discussed in a previous paragraph. It is generally but not invariably successful in these objectives, although it is rather toxic.

Historical.—Plasmoquine was the first substance, outside of quinine and its immediate derivatives, shown to possess distinct antimalarial properties. Its synthesis by Schulemann, Schönhöfer and Wingler, and its introduction as an antimalarial agent by Mühlens and Fischer in 1926, was the achievement of a systematic search for quinine substitutes by the I. G. Farbenindustrie, involving well over a thousand compounds (review, J. H. Williams, 1942).

Fate and Excretion.—The excretion is slow. Considerable amounts are destroyed in rabbits, much less in cats and dogs (Le Heux and von Wijngaarden). Quinacrine interferes with the destruction and therefore increases its plasma concentration to several times the control level. This accounts for the increase of toxicity (T. J. Kennedy *et al.*, 1946).

Clinical Toxicity.—Restricted doses do not produce tinnitus or nausea, but large therapeutic doses may be seriously toxic. Death has occurred with 0.4 and 0.6 Gm. (Cordes, 1927). The individual susceptibility is not predictable, except that it is increased by quinacrine. The usual symptoms are headache and giddiness, cyanosis by methemoglobinemia (Fischer and Weise, 1929), nausea and vomiting, jaundice, sometimes severe abdominal pain, collapse in the more serious cases (J. B. West and Henderson, 1944). Convalescence is protracted. *Hemolytic anemia* occurs in about 5 per cent of the patients, after three to five days of therapy, sometimes gradually. It has no relation to the plasma level or to the presence of malaria or fever. It generally clears promptly on withdrawal (D. P. Earle *et al.*, 1946), but it may hamper recovery from malarial anemia. *Granulocytopenia* is frequent in patients with high dosage. It gradually returns to normal on withdrawal. Other leukocytes are not affected (Zubrod, Knowlton *et al.*, 1946).

Toxicity to animals varies with the species, cats being especially sensitive. Acute circulatory collapse predominates with rabbits; cats and dogs succumb more gradually to methemoglobinemia (Le Heux and van Wijngaarden, 1929). Tskimonauri, 1931, reported that therapeutic doses (0.3 mg. per Kg.) raise the blood pressure and stimulate the respiration. Larger doses lower the pressure and produce dyspnea. The heart was relatively resistant. Eichholtz, 1929, found that intravenous injection of 2 to 3 mg. per Kg. results in A-V block. Pamaquine is not directly antipyretic, for coli fever in rabbits is affected only by toxic doses (Girndt, 1929). The uterus is probably not affected by therapeutic doses. Higher concentrations stimulate, and toxic doses depress (Epstein, 1933). Oral administration to dogs for three to six days induces ocular symptoms, enophthalmos, miosis, relaxation of nictitating membrane, suggesting central depression of sympathetic tone (Moe and Seevers, 1946).

PREPARATIONS.—*Pamaquine naphthoate, Plasmoquine, Plasmochin, Aminoquin Naphthoate*: a yellow powder, practically insoluble in water, nearly tasteless, but with a local anesthetic effect when placed on the tongue. *Dose*, 10 to 30 mg. per day, as pill or capsule.

8-aminoquinolines related to pamaquine hold out promise of curing vivax malaria (R. F. Loeb, Clark *et al.*, 1946). **Pentaquine,** "SN 13,276," 6-methoxy-8-(5-isopropylaminoamylamino)-quinoline is more potent and less toxic than pamaquine, and in conjunction with quinine it appears to cure Southwest Pacific vivax malaria.

Certuna, α-dialkylamino-oxyquinnyl butane, has a clinical gametocidal action similar to that of pamaquine (Kikuth, 1938).

Paludrine ("4888"), an isopropylbiguanide derivative synthesized by Curd and Rose, 1945, is reported to effect clinical cure of vivax malaria, without serious side effects (A. R. D. Adams and Macgraith, 1945).

QUINIDINE

Quinidine, one of the cinchona alkaloids, is the dextro-isomer of quinine, the latter being levorotatory. The actions of the alkaloids agree qualitatively, but quinidine is rather less effective against malaria. Both alkaloids lower the contractility of skeletal and cardiac muscle, and lengthen the refractory period, but with quinidine the depression of contractility is less, and the prolongation of the refractory period relatively greater. It is a valuable agent for controlling auricular fibrillation, especially when this is not due to anatomic lesions.

The *fate* of quinidine is similar to that of quinine. When it is administered by mouth, the capillaries of the liver remove a part from the blood and hold it adsorbed (Bellet, Ravdin and McMillan, 1933). With intravenous injection about 95 per cent leaves the blood stream in five minutes, and 99 per cent within an hour (S. Weiss and Hatcher, 1927).

The effects on skeletal muscle throw light on the mechanism of the cardiac actions: Immersion in quinidine solution (1:25,000) lengthens the refractory period, so that the muscle does not respond to rapid stimulation by the usual tetanus, but by a relatively slow, independent rhythm of contractions followed by a complete relaxation (J. G. Brody and Sollmann, 1923). Such a rhythm would be more favorable to the performance of external work, such as pumping, than the continued tetanus, which consumes more energy, but dissipates it as heat. The latter is essentially the condition of the fibrillating auricle.

Quinidine also suppresses the physostigmine twitching of skeletal muscle in cats (S. Weiss, 1926); it slows markedly the rate of fibrillation of the tongue after hypoglossal section. (This approximates the rate of auricular fibrillation. It is quickened by strophanthin; Buchbinder, 1930). The force of the contractions of the muscle tends to be depressed by quinidine, although not so much as by the quinine; but this is largely compensated by the rest in the refractory pause. Quinidine, quinine, cinchonine and cinchonidine act essentially alike upon striped muscle, but with quantitative differences of practical importance (Brody and Sollmann, 1923; Santesson, 1892; Secher, 1915).

Effects on Normal Heart.—Effective doses of quinidine (or quinine) prolong the refractory phase and thereby slow the conduction and the rhythm. The slowing permits greater filling of the heart, so that the amplitude is increased (Bodo, 1928). The carotid sinus reflexes are diminished or abolished, in man (by 2 Gm.; Nathanson, 1934) as well as in animals (Vercauteren, 1932). *Brief fall of blood pressure* is a constant characteristic of the *intravenous injection* of quinidine, but is apparently quite independent of the cardiac effect and possibly a flocculation phenomenon. The pressure in the pulmonary artery rises with small doses, but with large doses it falls more than the systemic blood pressure does. *Toxic doses* impair the heart, producing sinoauriculo or auriculoventricular block or ventricular fibrillation, or gradual inhibition of the whole heart; the auricles usually cease after the ventricles.

Analysis of the Cardiac Actions.—Intravenous injection of therapeutic doses (5 to 10 mg. per Kg,. corresponding to 5 to 10 grains in man) into normal animals (especially dogs) produces the following effects (Th. Lewis *et al.*, 1922; H. M. Korns, 1923; D. E. Jackson *et al.*, 1922; Cohen and Levy, 1921).

Prolongation of the refractory period, by 50 to 100 per cent. This explains the other phenomena in a large part, if not altogether.

Depression of excitability, i. e., higher threshold of stimulation; greater resistance to extrasystoles; disappearance of extrasystoles (the latter discovered for quinine by Starkenstein, 1907); relief of aconitine and barium irregularities. The decreased excitability is largely a manifestation of the increased refractoriness.

Slowing of the rhythm, sometimes after a temporary acceleration. The rate of the atropinized heart (135 to 190) may be slowed by 30 to 80 beats per minute. This also results from the refractoriness.

Increased amplitude of excursions (16 to 100 per cent), due to greater diastolic filling which results from the longer diastolic pause; therefore, also the result of the lengthened refractory state. The systolic volume is not altered by these doses.

Inconstant effects on the T wave; frequently reversed and changed in volume.

Slowed conduction, auriculoventricular, and also within the auricular and within the ventricular muscle. Toxic doses may produce a 2:1 auriculoventricular block.

Inconstant alterations in the response to vagus stimulation.—Jackson *et al.* found the response generally increased. Lewis *et al.* found little effect on the response of the sinus rate, but the decrease of A-V conduction normally produced by vagus stimulation was materially smaller under quinidine, and in some cases vagus stimulation produced even an increase of conduction. This "vagus" reversal was studied by Dale, 1922, who considered it analogous to the effect of nicotine and curare, and distinct from that of atropine.

For blocking cardiac inhibition by maximal vagus stimulation in dogs, quinidine is twice as potent as cinchonidine and cinchonine, and three times as potent as quinine, referred to plasma concentrations (Hiatt, Brown *et al.*, 1945).

The *frog heart* is depressed by quinine (Santesson): the heart is slowed by 1:50,000 solution and weakened in its contraction; its effectiveness is consequently diminished. The slowing occurs after atropine, and is therefore muscular. A 1:5000 solution kills the heart in a few minutes. Segments of the apex of the ventricle also respond by weakened contractions, and increased refractoriness is shown by higher resistance to tetanization (Sasaki, 1921). In strong solutions the dextrorotatory cinchonine and quinidine are less depressant than the levorotatory quinine and cinchonidine (McK. Cattell and Cattell, 1926).

Turtle Heart.—Electrically driven segments of the auricle and ventricle respond to quinidine chiefly by increased threshold for electric stimulation. The conduction of the muscle is raised. The refractory period is not materially altered in these preparations (Wedd *et al.*, 1942). In intact hearts, all the cinchona alkaloids diminish the amplitude and frequency, ending in diastolic arrest. The levo-bases (quinine and cinchonidine) are more toxic than their dextro-isomers (Fredericq and Terroine). W. S. Love, 1926, reported that both quinidine and strophanthin cause a slight shortening of the refractory period in the intact turtle heart. On this basis, Lewis and Drury, 1926, interpreted the prolongation of the "effective refractory period" under quinidine, strophanthin and veratrine as concerned with the spreading of the impulse rather than with local recovery of excitability.

Perfused Mammalian Heart.—F. B. Hofmann, 1920, found considerable increase of the resistance of the auricles to electric extrasystoles and fibrillation under quinidine. It also lowered the force of the contractions, without much change in rate. Larger doses abolish the contractions and render the muscle inexcitable. Further studies were made by Boden and Neukirch, 1921.

Quinidine against Auricular Fibrillation.—The lengthening of the refractory period is utilized clinically to combat auricular fibrillation (Th. Lewis, 1922; Clerc and Pezzi, 1922; H. M. Korns, 1923). Quinidine gradually slows the high rhythm of the auricles, and in about half the cases this terminates in a sudden cessation of the fibrillation and return to the normal heart rhythm. While the auricular oscillations are slowing, the ventricular contractions increase in regularity, but also in rate, toward a 1:3 or 1:2 rhythm, until the normal rhythm is restored. This may be attained in one to three days, sometimes with only a total of 0.6 Gm. of quinidine. The normal rhythm may then persist indefinitely without medication. In other cases the quinidine medication must be maintained continuously day and night; and in others again the quinidine fails to break up the fibrillation.

Mechanism of Quinidine in Auricular Fibrillation.—The prolonged refractory state tends to render the auricular muscle incapable of maintaining the rapid rate characteristic of fibrillation. It also tends to break up the circuits of auricular excitation which Garrey, 1914, and Lewis, 1921, considered the mechanism of the rapid rate; for the wave of excitation would die out when it found the muscle inexcitable on completing the circuit; and with the cessation of these stimuli, the sinus rhythm would resume its pace-making function. The auriculoventricular block resulting from the excessively numerous stimuli would diminish; partly because fewer stimuli arise and partly because the refractoriness of the bundle would also be increased by the quinidine, so that it would not be affected by the majority of the stimuli. The stronger and more regular impulses set a pace that the ventricles can follow; at first, imperfectly, *i. e.*, with a partial block. So long as fibrillation persists, this blocked ventricular rhythm would be faster than the more completely blocked rate that obtained before the quinidine; but the ventricular rhythm would be much more regular, and much more efficient for the propulsion of the blood. When the circuit of fibrillation or the unfavorable cycle of rapid rate:short refractory period, is broken and the normal length of the pendulum of strong refraction and strong contractions is reestablished, the latter tends to perpetuate itself automatically. If the original cause of the fibrillation persists, it may reproduce the fibrillation when the quinidine has been excreted, and continuous administration may be necessary. In nearly half the cases quinidine is unsuccessful. It is conceivable that the conduction may sometimes be so much slowed that the excitability of the muscle is restored before the circuit is completed, notwithstanding the prolonged refraction; but the failure may sometimes be due to failure to reach and maintain an adequate dosage, because of fear of the dangers of the drug. Failure is most frequent in cases of long standing, with marked cardiac insufficiency. The most favorable cases are those of short duration or of paroxysmal type.

Administration.—Quinidine sulfate may be administered in capsules or tablets. The susceptibility of the patient is tested by a dose of 0.2 Gm., which is repeated in two hours. If there are no bad effects, the regular dosage is started on the following day, with 0.2 to 0.4 Gm. three to five times per day, generally not exceeding 2 Gm. per day. If no benefit follows within three days, quinidine is generally considered unsuccessful and its administration is stopped. In case of complete success, the drug may be omitted, and readministered on recurrence. The maintenance dose is about 0.25 Gm. per day. If toxic manifestations occur, it should be discontinued. Prolongation of the Q-T interval furnishes a criterion of quinidine action. With 0.2 to 0.35 Gm., the full action is attained in one and one-half to three hours (also with intramuscular injection). It fades in eight hours. Administration at two hour intervals gives cumulation (Sagall *et al.*, 1943).

Previous digitalization may perhaps increase the chances of success and diminish the danger of accidents. It prevents the ventricular tachycardia that sometimes occurs in quinidine therapy (T. Lewis *et al.*, 1922). Quinidine is more depressant and toxic to skeletal muscle when this is overloaded and fatigued. Presumably this holds also for the heart, and would be counteracted by digitalis. On the other hand, digitalis would reinforce the beneficial lengthening of the refractory period. Conversely, quinidine counteracts the "toxic irregularities" of digitalis (C. C. Haskell, 1928; Kwit and Gold, 1934). It is well to observe that the two drugs produce prolonged refraction and slowed conduction by absolutely different mechanisms: the digitalis by the increased force of the preceding contraction, the quinidine by the slowing of the restorative metabolism.

Accidents.—In susceptible individuals, quinidine may produce phenomena similar to those of quinine hypersusceptibility, *i. e.*, nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. Occasionally, but rarely, quinidine may change auricular fibrillation to more serious irregularities, intra-auricular block, ventricular tachycardia and fatal ventricular fibrillation. The frequency of fatal incidents in auricular fibrillation is no greater with than without quinidine (Viko, Marvin and White, 1923; H. L. Smith and Boland, 1939). Cumulation need not be feared, since quinidine is rapidly excreted.

Other cinchona alkaloids have the same effect in auricular fibrillation, and are interchangeable with quinidine within a limited range, but their action is not so potent, regardless of dosage (H. Gold, Modell *et al.*, 1946).

Synthetic substitutes have been studied for cardiac actions by G. S. Dawes, 1946.

Ventricular Fibrillation.—Mautz, 1936, found quinidine effective in reducing cardiac irritability in surgical operations on the heart. Wégria and Nickerson, 1942, 1943, showed that it raises the fibrillation threshold to faradization and to epinephrine.

Use in Other Cardiac Irregularities.—R. W. Scott, 1922, found the continued administration of quinidine completely successful in arresting and preventing *ventricular tachycardia.* Pezzi and Clerc, 1930, reported favorable clinical effects from quinine against extrasystoles, paroxysmal tachycardia and auricular fibrillation. They administered 0.5 Gm. by mouth, two or three times per day. J. H. Wyckoff and Otto, 1926, found quinine ineffective in patients who responded to quinidine. Quinidine was effective in preventing attacks of *paroxysmal auricular tachycardia,* both spontaneous and induced by epinephrine (H. L. Otto and Gold, 1926). This may require larger doses, but 2 Gm. of the sulfate per day generally suffice, and may be continued for weeks without evidence of injury; however, as much as 4.8 Gm. (0.6 Gm. every three hours) is sometimes needed. It does not slow the rate of *sinus tachycardia,* including that of *thyrotoxicosis;* but it is effective against auricular fibrillation in this condition (P. S. Barker *et al.*, 1943).

PREPARATIONS.—***Quinidine Sulfate,** U.S.P. (Quinidin. Sulf.), $(C_{20}H_{24}O_2N_2)_2.H_2SO_4.2H_2O$, occurs as needle-like white crystals, very bitter, soluble in water (1:100). Average dose, 0.2 Gm. *Quinidine Sulfate Tablets,* U.S.P.; usual sizes, 0.1, 0.2 and 0.3 Gm., 1½, 3 and 5 grains.

HYDROCUPREINE DERIVATIVES

The alkyl derivatives of hydrocupreine were found by Morgenroth to have a high bactericidal efficiency, even in the presence of protein; and at the same time a relatively low toxicity to the tissue cells. They were therefore proposed as tissue antiseptics, both for local and systemic application. The germicidal power varies specifically for different bacteria. Ethylhydrocupreine ("optochin") is especially toxic to pneumococci; while higher homologues, such as "eucupine" and "vuzin" are more efficient against pus organisms. The effects of various new derivatives on *pneumococci in vitro* and on guinea pigs were reported by Gundel and Seitz, 1933. Eucupine and vuzin were introduced by Morgenroth, 1917, as wound antiseptics. Enthusiastic reports were published, especially in the German army. They were also employed in pleural empyema; but their use has not spread. Their pharmacologic actions agree in most respects with those of quinine. The literature is reviewed by Bijlsma, 1920, and Bruhn, 1919. Eucupine is iso-amyl hydrocupreine (the alkyl replacing the first C_2H_5 in the quinoline); and vuzin is iso-octyl hydrocupreine.

ETHYL-HYDROXYCUPREINE (OPTOCHIN)

This drug has a special toxicity for *pneumococci* (Morgenroth and Halberstaedter). It is successful against experimental pneumonia in mice, but much less successful in man (Moore and Chesney, 1918). Its application is further limited by the fact that efficient doses are liable to produce retinitis and blindness. It appears to be of some value locally in pneumococcic infections of the eye.

Ophthalmic Use.—Optochin hydrochloride is used locally as antiseptic, irritant and anesthetic in conjunctivitis, and on ulcers, especially ulcus corneae serpens. A fresh 1 or 2 per cent solution is applied, at first every two hours (Bedell, 1920). The first instillation is painful, but this is followed by *local anesthesia,* lasting one-half hour or longer (Morgenroth and Ginsberg, 1912 and 1913). Weaker concentrations are ineffective; 1 per cent does not cause permanent damage, but stronger solutions injure the cornea. Subconjunctival injections of ½ to 1 per cent also produce local injury (R. Schneider, 1920).

Bactericidal Action on Pneumococci.—*In vitro,* the drug inhibits the growth of pneumococci with a concentration of 1:800,000 in serum; it kills them with 1:400,000 (Wright, 1912). The action is slow with low concentrations, and increases in speed with the concentration. Serum reduces the activity to ⅕ or ⅒ (Cohen, Kolmer and Heist, 1917). Solutions in blood are even less active than those in serum; but the entire blood is more active than the serum separated from it, since the corpuscles take up a higher percentage of the drug (Morgenroth, 1918). All strains of pneumococci, as also some streptococci, are inhibited *in vitro* by concentrations of 1:100,000; whereas other streptococci, meningococci and gonococci require 1:10,000-5000. However, transition races are occasionally found. Quinine requires much higher concentrations. Optochin also increases greatly (potentiates) the efficiency of antipneumococcus serum (H. F. Moore, 1915).

Phagocytosis.—Optochin (and quinine) accelerate the phagocytosis of pneumococci (Cohen *et al.*).

Experimental Pneumonia.—Morgenroth, 1911, found optochin more effective than quinine against trypanosome and pneumococcus infections of mice. With these, optochin is effectively prophylactic in 90 per cent, and curative in 50 per cent of the experimental infections (Morgenroth and Levy; Engwer, 1912). The serum of rabbits is bactericidal after hypodermic doses of 0.1 Gm. per kilogram, which are well tolerated. Larger doses are usually toxic. Oral administration is not so effective (Moore, 1915).

Blindness occurs frequently, even with the ordinary therapeutic doses, such as 1.5 Gm. per day. Fraenkl, 1915, obtained some degree of amblyopia in 10 per cent of his series. The disturbance of vision generally starts abruptly and is usually severe, often progressing to complete amaurosis. The pupils are maximally dilated. If the drug is stopped, the vision usually improves, after a few days, but sometimes only after months; and even in the more favorable cases there remains more or less restriction of the visual field, central scotoma and impaired color vision (literature, A. Adler, 1916).

The *pathology* is similar to that from quinine (literature, Adler, 1913; experimental, Hirschfelder, 1915).

Other Side Actions.—The susceptibility to these varies greatly in different individuals. Temporary cinchonism and vomiting are frequent (Seifert, Nebenwirk, 1915).

Administration.—The daily dose of 0.024 Gm. per Kg

(1.5 Gm. per 60 Kg.) should be divided so that a fraction (*i. e.*, 0.15 Gm.) is taken every two and one-half hours, to maintain a constant concentration in the blood. There is a slight accumulation, and the drug should not be continued more than three or four days. The vision should be carefully tested throughout.

Other Infections.—Izar and Nicosia, 1914, used it against malaria because the cinchonism is shorter than with quinine. Levy, 1912, also claimed a curative effect against Streptococcus mucosus.

Hay Fever.—Hacke, 1919, reported good results from swabbing with 1 per cent optochin hydrochloride. Confirmation is required.

The **pharmacologic actions** correspond qualitatively with those of quinine, but are more toxic. Intravenously, optochin is more depressant to the heart; the blood pressure, however, falls less than with quinine, since there is also vasoconstriction (Smith and Fantus, 1916; Doeschate and Laeuwen, 1917). The antipyretic efficiency of optochin is smaller (Smith and Fantus). It has but little inhibitory action on the emigration of leukocytes (Ikeda, 1916).

Fate.—The alkaloid disappears rapidly from the plasma after intravenous injection. It persists longer and in greater amount in the corpuscles (Boecker, 1915).

PREPARATIONS.—*Ethylhydrocupreine Hydrochloride*, N.F., *Optochin*. Very soluble in water (1:2).

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ANTIPYRETIC ANALGETICS

Certain groups of pyrrole, benzene, aniline and quinoline derivatives are antipyretic, increasing heat loss in fever, mainly by mobilizing water, like the nonspecific action of quinine. They also relieve the discomfort of "colds," and the pain of headache, dysmenorrhea, neuralgias, neuritis and rheumatic conditions, but they are not very effective against acute traumatic pain. They are often harmless, but may develop toxic reactions with little or no warning, and some are subject to allergy. This group of drugs includes the pyrazolon derivatives, antipyrine and aminopyrine; the paramidophenol derivatives, acetanilid and acetophenetidin (phenacetin); the salicylates and the quinoline derivative cinchophen.

The **antipyretic action** is discussed under Temperature Regulation (see Index). In general, the extent of the antipyretic action increases with the dose of the drug from the smallest effective dose (0.2 Gm. for acetanilid, 0.5 to 0.7 Gm. for antipyrine or acetophenetidin), until the normal temperature has been reached. Up to this point there is little danger of a direct collapse action. But if the dose necessary to secure this result is exceeded, the toxic effects set in. The *full antipyretic* dose may be stated as 0.5 Gm. (7 grains) of acetanilid; 0.8 Gm. (10 grains) of acetophenetidin, 1 Gm. (15 grains) of antipyrine.

In beginning the treatment, this dose has to be repeated once or twice, with an hour's interval, until the desired fall is secured. After this, the single dose is repeated whenever the temperature begins to rise. Four or five doses are required per day to keep the patient practically fever free. The action does not persist after the drug is excreted. With single doses the antipyretic effect reaches its maximum in about two hours, and then declines gradually, so that the febrile level is practically restored in eight hours (Gottlieb, 1890). *Synergism by magnesium* with the antipyretic action of this group was reported by Barbour, Winter and Richey, 1930.

Undesirable side actions are rather common, especially when full antipyretic doses are used. Susceptibility to these differs. *Sweating* and *chills* are part of the temperature regulation. Nausea and other phenomena of *cinchonism* are necessary concomitants of full salicylate dosage (salicylism), but are exceptional with the others. Sodium salicylate rarely has other material side actions, but it may produce temporary renal irritation. Large doses of acetanilid may cause *cyanosis*. *Skin eruptions*, including generalized erythema, urticaria and angioneurotic edema, occur especially with antipyrine and aminopyrine. Free salicylic and acetylsalicylic acid tend to produce *gastric irritation* and acidosis and may require to be guarded by alkalis. Collapse may occur, with weak and irregular pulse, dyspneic or shallow respiration, pale or cyanotic skin, cold sweat, disturbed consciousness, subnormal temperature, and death by circulatory failure. The collapse action is strongest in the "mother substances"—aniline, quinoline, phenetidin, phenylhydrazine, and phenol—and generally in the members of the antiseptic group; so strong, indeed, that the action of these cannot be safely controlled. Of the more usual antipyretics, acetanilid produces probably the strongest direct collapse effects; then comes antipyrine, then acetophenetidin, then salicylates. Direct collapse, however, is rare if the dosage is kept within reason. Sometimes it is due to the reduction of the febrile temperature, "unmasking" a preexisting febrile collapse. Caution is necessary in the use of all antipyretic measures in asthenic fevers. Menstruation also favors the development of collapse. *Allergic reactions* of various kinds may occur, including edema of the mouth and respiratory passage (asthma), especially with acetylsalicylic acid; malignant *neutropenia* with antipyrine and aminopyrine; and *hepatitis* with cinchophen. They will be considered under these drugs. The *treatment of acute poisoning* by overdoses of the antipyretics is by evacuation and stimulants, heat, and so forth. The **analgetic action** is secured by relatively small doses, such as acetylsalicylic acid, acetophenetidin or aminopyrine, 0.3 Gm., 5 grains; acetanilid, 0.2 Gm., 3 grains; acetylsalicylic acid, 0.3 Gm., 5 grains; sodium salicylate, 0.6 Gm., 10 grains; repeated in three hours, if necessary. If these doses fail, larger doses are usually also ineffective, except in rheumatic fever, where the dosage must be pushed to salicylism. The *mechanism of the analgesia* is obscure. It may occur without dulling of consciousness, nor do antipyretics reinforce the actions of ordinary narcotics to a marked degree (Lomonorsoff, 1911). The appreciation of tactile sensations or of traumatic pain is but little dulled. The effect on headache may be due to relief of intracranial pressure by mobilization of excess water, as in the antipyretic action; it may be imagined that something of the kind takes place in the relief of neuralgia.

Analgetic efficiency may be measured in man by the amount of heat radiation necessary to produce pain when applied to the skin of the forehead. This threshold is raised by analgetic drugs to a certain limit. The following are the average doses required to produce the maximal analgesia of which the drug is capable, and the average per cent by which this raises the pain threshold: Dilaudid, 3 mg., or metopon, 6.6 mg., or morphine sulfate, 30 mg., each *100 per cent;* codeine phosphate, 60 mg., *50 per cent;* ethyl alcohol, 30 cc. or trichlorethylene inhalation, *40 per cent;* acetanilid, acetophenetidine or acetylsalicylic acid, or aminopyrine, 0.5 Gm., *35 per cent;* evipal, 0.5 Gm., *20 per cent;* caffeine or quinine or ergotamine, *none.* Combinations are merely additive. Higher doses increase the duration, but not the degree of analgesia. The appreciation of heat as such is not decreased by salicylate. *Suggestion* with a placebo may raise the threshold by 30 per cent. *Prejudice,* anxiety and doubt may make acetylsalicylic analgesia practically ineffective (H. G. Wolff *et al.,* 1940, 1942, 1943). By a similar method (D'Amour and Smith) applied to rats, the analgetic potency in comparison with acetylsalicylic acid (= 1) is: aminopyrine, less than 0.6; acetophenetidin, 0.8; antipyrine, 2.0; acetanilid, 2.6; sodium salicylate, 3.6; salicylamide, 7.5 (E. R. Hart, 1946).

Psychologic Experiments on Man.—Quinine, antipyrine and acetophenetidin in doses of 1 Gm. produce marked impairment in mental efficiency tests (Muensterberg, 1892). Analgetic doses (0.025 to 0.5 Gm.) do not impair neuromuscular coordination, as judged by the "tapping test," but they retard the reaction time (Macht *et al.,* 1918).

Sensations other than pain are not materially affected by therapeutic doses of analgetics (acetylsalicylic acid, opiates, alcohol, barbiturates; Wikler *et al.,* 1945). *Cutaneous sensibility,* when tested with bristles, shows only slight and questionable changes. Some experimenters report increased threshold (Martine *et al.,* 1915; Hale and Grabfield, 1923; P. K. Smith, 1937); but Mullin, 1937, found no significant effect on cutaneous tactile and pain sensation, not even when headache was relieved. The *acuity of hearing* is decreased by the salicylates, but rather increased by small doses of other antipyretics, including quinine (Macht *et al.,* 1920). The discrimination of musical pitch appears to be diminished by all.

Addiction to antipyretic analgetics would not be expected in normal individuals, as these drugs do not produce appreciable effects unless headache or other aches are present. In most cases, the habitual use is prompted and maintained for the relief of pain, headache or menstrual distress. It may develop toxic symptoms, especially cyanosis with acetanilid and acetophenetidin; but it is a superficial habit rather than a firm addiction, and withdrawal does not cause marked reaction. A few individuals feel euphoria, and these may develop addiction, with considerable reaction (restlessness and excitement, sometimes maniacal) on abrupt withdrawal (Payne).

Proprietary headache powders usually contain from 50 to 70 per cent of acetanilid or acetylsalicylic acid, or mixtures of these, often with caffeine, bromides, ammonium carbonate or sodium bicarbonate. The caffeine and bromide may reinforce the analgetic action. Mixtures of acetophenetidin, acetylsalicylic acid and codeine are said to be somewhat less toxic than would correspond to the sum of their components (S. Loewe *et al.,* 1927), but this requires confirmation. The alkalis were supposed to increase the solubility, but do not do so (Puckner, 1906). It was also claimed that all these drugs diminish the toxicity, but even caffeine lacks this effect (E. D. Brown and Moorehead, 1925). The indiscriminate use of the powders by the laity has repeatedly produced acute and chronic poisoning. The use of aminopyrine in such powders, which is especially dangerous, has greatly diminished. When the new Food and Drug Regulations became effective, the sale of acetanilid in the United States decreased from 986,000 to 427,000 pounds between 1937 and 1939, while the sale of acetylsalicylic acid increased from 2,500,000 to 5,300,000 pounds.

Synergism with Hypnotics.—Small doses of the antipyretic analgetics, including quinine, augment somewhat the sedative effect of hypnotics and perhaps conversely (Starkenstein, 1925; Loewe, 1927; Steinmetzer, 1928). Mixtures of aminopyrine and various barbiturates had a considerable vogue before the casual connection of aminopyrine to granulopenia was realized. The practical advantage of such combinations is probably not great. Pohle and Nietschmann, 1938, believe that the analgetic action is weakened, not potentiated.

Barbiturates decrease the acute toxicity of amino pyrine by a third (C. L. Rose, 1935), but aminopyrine does not confer protection against barbiturate (Pohle and Nietschmann, 1938).

PYRAZOLON DERIVATIVES: ANTIPYRINE (PHENAZONE) AND AMINOPYRINE (PYRAMIDON)

These are feeble bases, readily soluble in water (antipyrine, 1:1; aminopyrine, 1:18), differing in this respect from the acetanilid group. Antipyrine is used chiefly as antipyretic, and aminopyrine as analgetic (see the preceding section). The discrimination is perhaps merely traditional. Aminopyrine is about three times as potent as antipyrine. Its tendency to malignant granulopenia makes its use unsafe. Two to 5 per cent solutions of antipyrine are employed in the mouth and throat and in cystoscopy, and 0.4 per cent on the conjunctiva, for mild local anesthesia. This is preceded by smarting.

The **antipyretic action** has been discussed in the preceding sections on antipyretics (see Index).

Heat loss is considerably increased in normal animals, and the increase is several times greater in fever (Gottlieb, 1891). Calorimetric data show a moderate compensatory increase of *heat production*, more marked at normal temperature than in fever. The metabolism data are contradictory (review, S. Weber, 1904). Excessive doses (0.75 Gm. in rabbits) diminish heat production, presumably by incipient collapse. The *nitrogen metabolism*, with therapeutic doses and normal temperature, shows generally no change or some fall. Large doses often increase the nitrogen excretion, especially in man. In fever, therapeutic doses decrease the excessive nitrogen metabolism. Therapeutic doses with normal temperature produce no change or some decrease of *carbon dioxide metabolism*. Larger doses (2 to 3 Gm. of antipyrine for man) produce a small but unmistakable decrease in both gaseous exchange and nitrogen excretion (incipient collapse?). The effect on carbon dioxide metabolism is also inconstant in fever. Therapeutic doses may somewhat increase or diminish the CO_2 excretion, or leave it practically unchanged. *After the fall of temperature has set in*, the carbon and nitrogen metabolism are commonly lowered. This may be ascribed to the removal of the hyperpyrexia, for metabolism is naturally less active at the lower temperature. Antipyrine, and especially phenacetin and acetanilid, decrease the arterial oxygen; the CO_2 is less changed (Piccini, 1912). The *respiration of excised muscle* is not affected by antipyrine (in contrast to quinine and salicylate) unless high concentrations are used (Senta, 1908). The oxygen uptake of rat tissue is diminished by 20 to 30 per cent when aminopyrine, M/4500, is added. Antipyrine is inactive (Bernheim, 1939).

Side Actions.—Large doses of antipyrine and its derivatives produce collapse effects essentially identical with those of the acetanilid group which may result in considerable fall, even of the normal temperature, proportionate to the metabolic rate (Githens, 1925). These drugs have less effect than acetanilid on blood, but are much more likely to cause skin eruptions.

Antipyrine Eruptions.—With susceptible individuals, these occur promptly even after small doses; in the form of round or oval erythematous somewhat pigmented patches, which may become bullous. When the drug is discontinued, these are replaced by pigmented areas, which become rapidly congested if another dose is taken (H. MacCormac). It has been claimed that the hypersusceptibility may be desensitized by small doses (Widal and Vallery-Radot, 1920).

Fate.—Antipyrine and aminopyrine are eliminated largely unchanged by the urine (Jonescu, 1906), partly as glycuronate, which reduces Benedict's reagent, but does not ferment with yeast (Enkelwitz, 1935). Traces are excreted by the sweat (Tachau, 1911) and sputum (Hofbauer, 1915). The urine volume is generally decreased. Occasionally the urine is blood-red, and green in reflected light (Penzoldt). Aminopyrine urine contains several derivatives, including rubaconic acid, which gives a red color to acidified urine (Halberkann and Fretwurst, 1940).

PREPARATIONS.—*Aminopyrine*, U.S.P. (Amidopyrine; Pyramidon), occurs as a white, crystalline, odorless powder; soluble in water (1:18) and alc. (1:1.5). Dose, 0.3 Gm., 5 grains, generally administered in tablets and only once a day. *Aminopyrine Tablets*, U.S.P., usually 0.3 Gm. ***Antipyrine** (Phenazone), is a white, crystalline, odorless, slightly bitter substance; sol. in water (1:1) and alc. (1:1.3). Incompatible with nitrites (Sp. Aeth. Nitrit.), tannins, calomel and sodium salicylate. Average dose, 0.3 Gm., 5 grains; maximum dose, 1 Gm., 15 grains; in solution, powders or capsules.

AGRANULOCYTOSIS: ITS CAUSATION BY AMINOPYRINE AND OTHER DRUGS

Agranulocytosis, agranulocytic angina, malignant neutropenia, or granulopenia, is a syndrome of blood changes, systemic symptoms and local lesions in the mouth and sometimes other mucous membranes. It often begins with severe pharyngitis and ulceration of the mucous membranes of the mouth and throat as in Vincent's angina, but with a different etiology and blood picture. The characteristic feature is a marked decrease of the polymorphonuclear neutrophile leukocytes, without significant decrease of the red blood cells and hemoglobin. There is marked prostration, and if the agranulocytosis becomes complete, the outcome is always rapidly fatal (four or five days), often by an intercurrent infection, presumably through loss of resistance. The mortality in untreated cases is nearly 75 per cent. The condition was first described as a clinical entity by W. Schultz, 1922.

Causation by Drugs.—R. R. Kracke, 1931, and Madison and Squier, 1933, noted that most cases of agranulocytosis were connected with the use of *aminopyrine* or its compounds, generally either in large doses or over long periods. Although this occurs only in a small proportion of its users, and therefore requires a special susceptibility, the causal connection is definitely established.

The incidence of agranulocytosis was highest when this drug was most widely used (Kracke and Parker, 1934); it has waned in the United States since the use has become restricted, and it has practically disappeared in Denmark, where aminopyrine is no longer sold (Kracke, 1938). Cautious administration of aminopyrine to susceptible individuals produces the disease at will (Sturgis, 1935; Dameshek and Colmes, 1936; Benjamin and Biederman, 1936). Kracke, 1938, estimated that about 80 per cent of the clinical cases are due to aminopyrine or its compounds.

Most of the remainder are due to other drugs, chiefly to dinitrophenol, arsphenamine, sulfanilamide and "novalgin" (a derivative of aminopyrine); more rarely to acetanilid, acetophenetidin, cinchophen, quinine, organic antimony compounds, and gold salts. A few cases probably occur without drugs. Barbiturates apparently do not cause it. The *hypersusceptibility* may develop suddenly after short or long usage (Holten, 1937). Once developed, it appears to persist indefinitely. It probably belongs to the group of conditioned toxicoses, which Landsteiner and Jacobs, 1935, suggested may be due to alterations induced in some tissue protein which render this antigenic. The bone marrow and blood appear to be rather subject to such reactions, as seen also in thrombocytopenic purpura, hemolytic anemia, pancytopenia and leukemoid reactions (Fitz-Hugh, 1938). The *susceptibility of animals* to the neutropenic action appears to vary as widely as that of man.

Kracke and Parker reported that the administration of these drugs to rabbits produces injury of the bone marrow, with decrease in the neutrophils, thrombocytes and blood platelets. Similar effects are produced in dogs (Butt *et al.*, 1939), but they require much greater doses, so that their identity with the clinical phenomenon is not certain. Interference with the normal leukocytic response to nucleic acid injection has been reported in rabbits treated with antipyrine and other drugs suspected of producing clinical leukopenia, with doses that did not lower the number of leukocytes in normal animals (Climenko, 1935); but the dosage was still far beyond the therapeutic range. D. K. Miller and Rhoads, 1937, reported that the bone marrow changes occur with smaller doses of aminopyrine in dogs with dietary insufficiency ("black tongue" diet). On the other hand, Stenn, 1935, found no change in the blood picture of numerous guinea pigs, rabbits and monkeys, kept for over eight months on aminopyrine, with doses so large as to cause diarrhea, stupor, malnutrition and some fatalities. The changes caused by hemorrhage, starvation, infections or benzene poisoning, were not modified by aminopyrine. Filo, 1937, reported that aminopyrine produces hemolytic and regenerative anemia in guinea pigs, with increase of reticulocytes, normoblasts and leukocytes, including granulocytes.

Pathology.—The blood changes start before the fever and necrosis of the mucous membranes, so that they are not caused by these. The primary lesion appears to be a "maturation arrest" ("anakmesis") in the bone marrow, which is filled with young granulocytes and is poor in mature cells (Darling *et al.*, 1936; Fitz-Hugh, 1938). Stenn, 1935, described degeneration of the myeloid cells. Parker and Kracke, 1936, reported that *glutathione* is depleted in leukopenic patients and animals and suggested that this agent may play an important part in regulating bone marrow activity, and that its deficiency may be the starting point of leukopenia (review, W. Dameshek, 1936).

Kracke and Parker found *quinone* ($C_6H_4O_2$) and *hydroquinone* especially active in rabbits. These occur among the products of decomposition of the benzol derivatives in the body, and these writers suggest that the different neutropenic liability depends on the facility with which these decomposition products, especially hydroquinone, are formed.

Treatment of agranulocytosis has been attempted by transfusion, and by stimulating the bone marrow through injection of pentonucleotide; but severe cases generally die in spite of this treatment, and light cases recover spontaneously. The most promising approach is through bacteriostatic agents, penicillin and sulfonamides. The grave dangers of agranulocytosis enjoin great care in the use of aminopyrine, especially in analgetic mixtures, which are likely to be taken in excess. It should be used only on patients of known tolerance, and then only in small doses and for short periods. It should be stopped immediately if pharyngitis develops, or if the neutrophils decrease.

PARAMINOPHENOL DERIVATIVES (ACETANILID, ACETOPHENETIDIN)

The antipyretic and analgetic actions and uses of these *"coal tar antipyretics"* are discussed in preceding sections. They are effective, but the antipyretic doses are liable to produce undesirable side actions, and their use is believed to entail some danger of circulatory collapse, especially with acetanilid, but this is rare. Their continued use against headaches may cause chronic poisoning, especially cyanosis. These drugs are relatively insoluble, and are therefore used as powders or tablets. Their taste is not seriously objectionable.

Structure and Antipyretic Action.—The large number of antipyretic benzene derivatives differ quantitatively in their actions, with definite relations to their chemical structure. Salicylate, acetophenetidin and acetanilid are the most useful representatives, and the others may well be spared. Manufacturers introduced almost numberless antipyretics; but the number of really new and valuable products is small. The great mass of this material consists of insignificant variations in the established products.

The antipyretic action resides in the benzene ring, but benzene (C_6H_6) itself is not antipyretic, because it cannot readily enter into reaction with the body cells; this capacity of reacting may be given to it by substituting for one of its [H] atoms an [OH] group, as in phenol, C_6H_5OH; or still more strongly by an NH_2 group, as in aniline, $C_6H_4.NH_2$ (phenylhydrazine, $C_6H_5NH.NH_2$ being stronger); or by both as in paramidophenol, $C_6H_4OHNH_2$.

These aromatic alcohols and amides are called the "mother substances" of the antipyretic drugs. They are strongly antipyretic, but they also produce collapse. Before they can be used in practice, this collapse action must be diminished. This may be done by replacing the [H], either of the [OH] or of the [NH_2], by other radicals; the reduction of toxicity is greatest if the substitution is made in the NH_2. These substituted compounds act only after the mother substance is liberated from them in the body. Their action is therefore more gradual, less violent, and more easy of control. The reduction of toxicity is greatest if the substituted radical is an alkyl; less if it is an acidyl. If several H atoms are substituted, the toxicity is less if both an acidyl and an alkyl radical are introduced, than if both radicals be of the same kind. The toxicity and the therapeutic qualities *both* diminish with the size of the introduced radical. The most useful is the ethyl (C_2H_5) or acetyl (C_2H_3O) radical; with the methyl or formyl group, the toxic action is too great; with larger groups, and particularly with aromatic groups, the compound becomes so resistant that the therapeutic action is reduced almost to nothing. These laws must be modified if the compound is decomposed in the stomach with liberation of the mother substance. The radicals must be introduced into the ring by substitution; the mere addition of acid radicals, forming salts, does not modify the properties of the original substance. Therefore aniline acetate ($C_6H_5.NH_2.HC_2H_3O_2$) preserves the original toxic action of aniline; whereas this is greatly weakened in acetanilid ($C_6H_5.NH.C_2H_3O$). The substitution of an H by I, Br or Cl, does not modify the antipyretic or toxic action of the original substance. *Para-acetylaminophenyl urethanes* were reported by Cox, Eikler and Shriner, 1931, to be rather feebly antipyretic and not hypnotic.

Fate.—The antipyretics are rapidly absorbed and excreted. Acetanilid, acetophenetidin and their derivatives are mainly oxidized to paraminophenol (Hinsberg and Treupel, 1894), which is probably the form in which they produce their actions (A. G. Young and Wilson, 1939). This is excreted in the urine, chiefly as paired compounds with sulfuric and glycuronic acids. In man, acetanilid is oxidized to para-acetyl aminophenol (Mörner, 1889). It gives the "indophenol reaction" in the urine.

Notwithstanding its limited solubility, *acetanilid* is absorbed practically completely by rabbits even with oral administration of 700 mg. per Kg. of body weight, corresponding to about 45 Gm. for man (Stanton and Agricola, 1937). Its absorption was also complete in monkeys receiving by mouth 100 to 400 mg. per Kg. daily for nine to eighteen weeks (P. K. Smith, 1940).

The oxidation of acetanilid to paraminophenol by *tissue suspensions* was studied by H. O. Michel *et al.*, 1937.

Therapeutic Uses.—The antipyretic and analgetic actions and dosage are discussed in a preceding section. Acetanilid and acetophenetidin are administered in solid form as powders, capsules or tablets. They occur as white crystalline powders, of a warm, not unpleasant taste.

Acetanilid was introduced clinically as antipyretic by Cahn and Hepp, 1886, The antipyretics have been used in *diabetes insipidus*, but they are not very effective. The *antiseptic action* of the antipyretics is not very potent, but they are sometimes used as antiseptic, astringent and *hemostatic dusting powders* (acetanilid; or antipyrine in 5 per cent sterilized solution). They are less poisonous and less irritating than iodoform; but toxic effects have been reported from the application of acetanilid to wounds. Acetanilid is a potent inhibitor of certain *enzyme systems* in the body (F. Bernheim, 1943).

Leukocytosis was believed to be produced by antipyretics, but Gehrig, 1915, found no effect. The migration of leukocytes from the inflamed mesentery of frogs is inhibited by antipyrine (Ikeda, 1916). Phagocytosis *in vitro* is also unaffected (Arkin, 1913).

Circulation.—The general circulation is but little affected by ordinary doses. They may slow the heart indirectly by reducing the temperature; this has sometimes been misinterpreted as cardiac depression.

The *cutaneous vessels* are dilated; the *intracranial vessels*, after a short dilatation, show a more persistent constriction, similar to that from caffeine or alcohol (E. Weber, 1909). Hirschfelder, 1915, described dilatation of the pial and retinal vessels, from acetanilid, antipyrine, amyl nitrite, caffeine, and alcohol. This tends to raise intra-ocular pressure, enjoining caution in glaucoma (Wessley, 1915). With *toxic doses*, the heart is first accelerated, and later slowed, by direct action upon the heart muscle. Strips of terrapin's ventricle are slowed and arrested by acetanilid (Carr, 1910). The *vasomotor center* is not affected by moderate doses (with the exception of the part controlling the cutaneous vessels). The *blood pressure* depends solely upon the cardiac action, being at first increased and later diminished. In doses producing collapse there is paralysis of the vasomotor system, and consequent fall of blood pressure.

Striped Muscle.—Immersion in acetanilid solution (1:5000) diminished the direct and especially the indirect excitability of muscle (Macht, 1919). Muscle immersed in dilute antipyrine solution preserves its excitability much longer than when immersed in Ringer's fluid (J. G. Brody, unpublished).

Narcosis.—Goldfish immersed in acetanilid solution, 1:2500, undergo deep narcosis, which is reversible for several days. This effect has not been noted with paraminophenol or with salicylates (Sollmann).

The **toxicity** is rather low, even with acetanilid. The clinical phenomena have been discussed. Fatalities have been reported from 0.6 to 50 Gm. (P. J. Hanzlik, 1940), but are exceptional with the lower doses. In a variety of *animals*, marked prostration, cyanosis and dyspnea begin with about 200 mg. of acetanilid orally per kilogram of body weight. Even with 800 mg. per Kg., half of the animals recover. This would correspond to about eighty times the ordinary therapeutic dose. The blood of animals dying of acetanilid does not contain sufficient abnormal pigment to account for the death (P. K. Smith, 1939; Lolli *et al.*, 1943).

There is *no evidence of cumulative action*, for daily administration of 200 to 400 mg. per Kg. to rats or monkeys over ten to eighteen weeks does not produce significant changes in growth, hemoglobin concentration, blood count and leukocyte count. Indeed, some tolerance develops, both to the depressant and to the analgetic effects. With daily doses of 500 mg. per Kg., there is impairment of growth or loss of weight and a significant decrease of blood count without change in the leukocytes (Helms, 1933; P. K. Smith and Hambourger, 1936; Stanton and Agricola, 1937; P. K. Smith, 1940). *Withdrawal* does not cause any "abstinence symptoms" (*i. e.*, no increase of discomfort erethismus in rats, Stanton and Agricola; monkeys, Smith, 1940).

Influence of Sodium Bicarbonate on the Toxicity of Acetanilid.—Conflicting results have been reported. The results of P. K. Smith, 1936, indicate a moderate decrease in toxicity (about 25 per cent), when two molecules of bicarbonate were administered with each molecule of acetanilid.

Clinical chronic acetanilid poisoning may occur from the continued use of acetanilid headache powders, generally over some years. The patients show a peculiar cyanosis, sometimes with the histologic blood changes of pernicious anemia; marked leukocytosis; cardiac weakness; progressive mental and physical debility. Methemoglobin may also appear in the urine (D. D. Stewart, 1905). *Anemia* may be severe, with hyperplasia of the bone marrow, but with rapid recovery on withdrawal (Meulengracht and Lundsteen, 1939). An individual predisposition is probably necessary to produce marked chronic acetanilid poisoning: A series of ten human subjects who took 4 grains (0.25 Gm.) of acetanilid three times daily for sixteen weeks showed no significant changes in blood, urine, or in renal and hepatic functions (Helms, 1933). The persistent use tends in itself to produce headache, thus establishing a vicious cycle. The *withdrawal of acetanilid* rarely causes abstinence symptoms, but S. Payne, 1935, reported craving and restlessness for a few days, and excitement, sometimes quite maniacal, allayed by small doses of the drug.

The *cyanosis* occurs constantly in animals poisoned by large doses of acetanilid or acetophenetidin. Clinically it is inconstant, but generally it develops gradually with continued use of these drugs, sometimes within a few days, increases progressively for weeks and fades slowly during two weeks after withdrawal. Unsaturation of 2 to 28 per cent of the hemoglobin of many persons using acetanilid was reported by W. D. Paul and Clark, 1935. Its mechanism is disputed. The blood may contain some methemoglobin and sulfhemoglobin within the corpuscle, involving generally 2 to 5 per cent of the hemoglobin; but several observers have failed to demonstrate either sulfhemoglobin or methemoglobin in their clinical cases, or even decrease of oxygen binding power, and are inclined to attribute the cyanosis to colored products of the oxidation of paraminophenol (Lundsteen *et al.*, 1938; Meulengracht and Lundsteen, 1939; A. Leslie, 1939).

The *acute blood pigment changes* were studied by P. K. Smith, 1939, in rats, comparing ⅔ M.F.D. of acetanilid, and equimolecular amounts of acetophenetidin, aniline, paraminophenol, sulfanilamide and sulfapyridine. All formed appreciable amounts of methemoglobin and sulfhemoglobin. Methemoglobin and sulfhemoglobin were in about equal amount with acetanilid and acetophenetidin; methemoglobin predominated with aniline and sulfapyridine; sulfhemoglobin with sulfanilamide. Paraminophenol produced less abnormal pigment than the other compounds. Methemoglobin formation occurs readily in dogs on oral administration of acetanilid, 0.1 to 0.3 Gm. per Kg. of body weight (T. R. Kruse and McEllroy, 1927). The acetanilid and acetophenetidin methemoglobin increases with the dose as a sigmoid curve. Cats appear the most sensitive species; man is about half as much, dog a fourth, rat a twenty-fourth, rabbit and monkey very little. Continued administration to man led to little or no cumulation of methemoglobin (D. Lester, 1943). Para-aminophenol and beta-phenylhydroxylamine also have sigmoid curves of methemoglobin formation (Lester *et al.*, 1943). Ortho-aminophenol is more potent than the para in forming methemoglobin. *Nitrosobenzene* is less potent than hydroxylamine (C. Petersen, 1941). *Alcohol* is reported to increase methemoglobin formation by aniline in cats (W. Heubner and Schwedtke, 1936). D. Snapper, 1925, reported that *sulfhemoglobin* is formed in patients or dogs receiving acetanilid or acetophenetidin, if hydrogen sulfide is being absorbed from the intestinal tract, by administering sulfur by mouth, or in digestive disturbances with intestinal putrefaction (Harrop and Waterfield, 1930).

Methemoglobin formation in shed blood proceeds more weakly than it does in the body. The relation of the methemoglobin formation to the chemic constitution of benzene derivatives was investigated by W. Heubner, 1913. It is much more pronounced in the mother substances, aniline, phenylhydrazine, and the like; it is stronger with acetanilid than with the other antipyretics. Paraminophenol forms a reversible oxidation-reduction system with its quinimine, $C_6H_4.O.\ NH$, which acts as a catalyst. Phenylhydroxylamine is not catalytic, but oxidizes irreversibly to azoxybenzene (W. Heubner *et al.*, 1923). *Lactophenin* produces *icterus* in over half of the patients, usually on the ninth to twelfth day of its use. It is probably of the retention type rather than hemolytic (Hanssen, 1916).

The monograph of Martin Groves (Hillhouse Press, New Haven, 1946) gives an extensive *bibliographic review* of acetanilid.

Preparations.—***Acetanilid,** U.S.P. (Acetanilidum; Antifebrin; Phenylacetamide), $C_6H_5.NH.CO.CH_3$. White, crystalline, odorless powder; soluble in water (1:190); liquefies with chloral or antipyrine. Dose, 0.2 Gm., 3 grains; maximum, 0.5 Gm., 8 grains, in powders or capsules. ***Acetophenetidin,** U.S.P. (Acetophenetidinum; Phenacetin), $C_2H_5O.C_6H_4.NH.CO.CH_3$, 1:4; white, odorless, nearly tasteless powder or scales; slightly soluble in water (1:1310); liquefies with chloral and antipyrine. Dose, 0.3 Gm., 5 grains; maximum dose, 1 Gm., 15 grains, in powders or capsules. *Acetophenetidin Tablets*, U.S.P.; usual sizes, 0.12, 0.2 and 0.3 Gm., 2, 3 and 5 grains.

SALICYLIC COMPOUNDS

Salicylic acid (ortho-oxybenzoic acid, $C_6H_4OH.CO_2H$, 1:2) and its compounds produce marked antipyretic and analgetic effects and striking relief of the phenomena of acute articular rheumatism. The systemic toxicity is relatively low, but large therapeutic doses produce the so-called "toxic" symptoms of "salicylism," resembling cinchonism. The different compounds act qualitatively similar, but present quantitative differences. The salicylates are excreted by the urine, partly free and partly combined. Free salicylic acid is an antiseptic, active irritant and slow corrosive.

Historical.—Salicylic acid was first prepared in 1838 by Piria from salicin, which had been isolated by Leroux. Cahours, in 1844, and Procter, prepared the acid from gaultheria oil. Kolbe and Lautemann produced salicylic acid synthetically from phenol in 1860, and Kolbe devised a commercial practical synthetic process in 1874. He also investigated its antifermentative action. It soon became established as a surgical antiseptic (Thiersch, 1875); antipyretic (Buss, 1875); and antirheumatic (Strickler, 1876).

Relation of Constitution to Antirheumatic Action.—Phenol, $C_6H_5.OH$, is quite inactive. Benzoic acid, $C_6H_5.CO_2H$, has a limited efficiency. The OH and CO_2H groups are both necessary, and must be in the ortho position to obtain the full efficiency. Derivatives, which can be converted into salicylic acid in the organism, are effective, in proportion to the ease of their conversion. Introduction of additional groups into the benzene nucleus, as in the cresotinic acids, does not disturb the action (May, 1909; Stockman, 1913).

Cresotinic acids were at one time blamed for the reputed higher toxicity of synthetic salicylates. In fact, however, they act similarly and have about the same toxicity as salicylic acid (Stockman, 1890, 1912; Waddell, 1911). They have a similar specific effect in rheumatic fever, although they are somewhat inferior. They have even been used therapeutically in doses up to 8 Gm. (Buss, 1876; Gatti, 1879; Demme, 1888).

Isomers of Salicylic Acid.—Meta- and para-hydroxybenzoic acids are practically inactive and nontoxic. These isomers are excreted in combination with sulfuric acid instead of glycocoll (Sherwin, 1918).

Salicyl Esters.—The desire to avoid the disagreeable taste and the gastric symptoms of the ordinary salicylates led to the introduction of esters and similar compounds, more or less insoluble, in which the salicyl radical is bound so as to be liberated only in the intestine or after absorption. These compounds have little or no direct action on the stomach, but they do not avoid the nausea and vomiting (Hanzlik, 1913), since these are chiefly central. In this respect they are not superior to sodium salicylate, which also does not produce direct gastric irritation, if properly guarded by bicarbonate. The taste is materially improved. The alkyl esters (methyl salicylate) are more efficiently absorbed from the skin and are therefore better for external use. The acyl derivatives (acetyl salicylic acid) have higher analgetic and antipyretic action and therefore a special field.

These compounds may be arranged under three types: 1. **Replacement of the H of the Hydroxyl by Acyl Radicals.**—To this type belong: acetylsalicylic acid (aspirin), $C_6H_4.O(COCH_3).COOH$, and the corresponding compounds of salicylic acid with methylene citric acid (*Novaspirin*); with salicylic acid (*Disalicylic Acid*); and with succinic acid (*Diaspirin*). 2. **Replacement of the H of the Carboxyl by Alkyl Radicals.**—Methyl salicylate, $C_6H_4.OH.CO_2(CH_3.)$, and the corresponding salicyl esters of ethyl (*Sal Ethyl*); of methoxymethyl (*mesotan*); and of monoglycol (*spirosal*). 3. **Replacement of the H of the Carboxyl by Phenyl Radicals.**—Phenyl salicylate (*salol*), $C_6H_4.OH.CO_4(C_6H_2)$ and the corresponding salicyl esters of naphthol (*betol*); of guaiacol; and of acetparamidophenol (*salophen*). To these may be added *salicin*, from which salicylic acid is formed in the organism.

"Natural" and Synthetic Salicylates.—It was formerly claimed that synthetic sodium salicylate, owing to the presence of supposed impurities, is more toxic and less efficient than that prepared from oil of wintergreen or birch. The evidence for this view did not stand critical examination. There need be no hesitation in employing the much more economical synthetic product (Report, Council on Pharmacy and Chemistry, 1913, J.A.M.A., *61:* 979).

Various impurities were announced in synthetic salicylates, but Hilpert, 1913, showed that the cheapest commercial samples are quite as pure as the most expensive. Waddell, 1911, proved that the effects of natural and synthetic salicylates on animals are quantitatively alike; and the cooperative clinical tests, instituted by the Council on Pharmacy and Chemistry showed that their effects on patients are indistinguishable (Hewlett, 1913).

Fate.—The salicylates are rapidly absorbed from mucous membranes, and circulate as such. Salicylic acid may be liberated in the stomach, but not in the blood or tissues. The esters are also readily absorbed from the intestines, partly after hydrolysis, partly without decomposition. Some absorption of the esters occurs from the intact skin. Salicylate is excreted in all the secretions (sweat, Tachau; none in the feces, Hanzlik; practically none in the bile, Halpert *et al.*, 1930), but by far the larger part appears in the urine, mainly free, but partly conjugated. A part is oxidized to dioxybenzoic acid and hydroquinone. The excretion begins within fifteen minutes, and is practically completed in six to forty-eight hours. The rapid excretion explains the need of large and frequent doses. Larger doses may color the urine green.

Absorption of salicylates starts promptly, but a part of sodium salicylate may remain a considerable time in the stomach, especially if it has been precipitated as salicylic acid. Sodium salicylate is absorbed from the rectum (Massol and Minet, 1908), though not so readily as by mouth (Fiedler, 1905).

Absorption of the Esters from the Alimentary Canal.—The insoluble esters pass rapidly through the stomach, without material change, and are gradually absorbed from the intestines (Burow, 1911, dogs with duodenal fistula). They are partly hydrolyzed and saponified, but a part is absorbed without decomposition. With full therapeutic ("toxic") doses the median percentage of unchanged esters in the urine of patients averaged about 25 per cent of the total salicylate in the urine, when acetylsalicylic acid was given; 6 per cent with salicylsalicylic acid; and only 0.2 per cent with methyl salicylate. Acetylsalicylic acid was found to be hydrolyzed in acid and in alkaline buffer mixtures within the physiological range (*i. e.*, in the stomach as well as in the intestines), but was fairly stable at neutral reaction. Salicylsalicylic acid and methyl salicylate underwent but little hydrolysis; they must be decomposed in the tissues rather than in the alimentary tract (Hanzlik and Presho, 1925).

Absorption from the Skin.—Free salicylic acid, sodium salicylate, methyl salicylate and some of the other esters, in ointments or alcoholic solutions, are absorbed by the skin, but less rapidly than by mouth (Sauerland, 1912). Salicylate can generally be demonstrated in the urine after clinical application of salicylic acid ointment or washes (Leslie-Roberts, 1928). Sodium salicylate is absorbed from the skin much less than free salicylic acid (Lenertowicz, 1914). Methyl salicylate is absorbed most effectively from aqueous suspensions (E. W. Brown and Scott, 1934), but the quantity would not be significant therapeutically.

Diffusion through colloid membranes is hastened by salicylic acid or sodium salicylate (Oswald, 1910; Hanzlik, 1912). Salicylic acid also enters living cells which are impermeable to most other acids (Harvey, 1914).

Quantity of Total Salicyl Recovered from Urine.—With therapeutically toxic doses of sodium salicylate, Hanzlik recovered about 80 per cent; with acetylsalicylic acid, a median of 9 to 37 per cent; with salicylsalicylic acid, 63 per cent; methyl salicylate, 51 per cent. The higher values reported by older investigators were due to faulty methods.

Normal Time of Excretion.—Blanchier, 1879, found that sodium salicylate, administered by mouth, appeared in the urine in fifteen to eighteen minutes; with doses of 1 to 2 Gm. the excretion was completed in twenty-two hours; with 4 to 5 Gm., in forty-four hours. After continued administration, the excretion persisted from three to eight days. In dogs, the excretion was relatively slow; in herbivora, somewhat quicker than in man. Gaulier, 1913, reported the excretion as completed in eighteen to twenty-six hours. After application of a salicyl ointment to the skin, the excretion lasted two days (Schumacher, 1909). The elimination after intravenous injection was studied by F. Mandel, 1908.

The *excretion in rheumatic fever* averages about 10 per cent less than in normal individuals; the deficit is greatest in the first ten to twenty hours of administration. It is not due to retention, or to differences of diuresis, but partly to excretion in the sweat, and chiefly to increased destruction. The percentage of salicyl in the blood and urine at this time is little more than half of that in normal subjects (Scott, Thoburn and Hanzlik, 1917). The excretion is diminished in chronic alcoholism and morphinism, tuberculosis and diminished renal efficiency (Scott and Thoburn, 1917). Purpus and Chebchowski report delayed excretion in *renal and circulatory diseases.*

Time of Excretion of Salicyl Esters.—Full therapeutic doses of acetylsalicylic acid required a median of nearly five days; salicylsalicylic acid and methyl salicylate, two to three days (Hanzlik and Presho, 1923 and 1925). Phenyl salicylate is excreted more slowly than the other esters (Pinczower, 1910).

Urinary Metabolites of Salicylic Acid.—Kapp and Coburn, 1942, isolated four substances from human urine: salicylic acid, 20 per cent; salicyluric acid, 55 per cent; gentisic acid, 4 to 8 per cent; and Baldoni's uraminsalicylic acid. About 25 per cent was conjugated with glycuronic acid. *Salicyluric acid* (Bertagnini, 1856) is a compound with amino-acetic acid, analogous to hippuric acid. Some observers have failed to find it (Hanzlik, 1916; Angelico, 1921). *Gentisic acid,* C_6H_3.COOH-$(OH)_2$, dioxybenzoic acid, is an oxidation product intermediate to hydroquinone, $C_6H_4(OH)_2$ (C. Neuberg, 1911). It causes the urine to darken on alkalinization (Lutwak-Mann, 1943). *Conjugation with amino-acetic acid* occurs with the OH group in the meta and para, but practically not in the ortho position; similarly with bromo, iodo and nitro groups. Conjugation with gylcuronic acid is affected in the same direction, but to less degree (Quick, 1932).

Distribution in Organs.—Blanchier, 1879, investigated this in dogs and found the salicyl in the saliva, bile, cerebrospinal fluid, articulations, and so forth. Nencki, 1895, found it in the bile, but not in the gastric juice. Olmer and Totiau, 1910, confirmed its presence in cerebrospinal fluid, its quantity being independent of the dose. Stockman, 1906, found none in the saliva, traces in sweat, and considerable in the joint fluid, blisters, bronchial mucus and pleural effusions. Scott, Thoburn and Hanzlik, 1916, found the percentage in joint fluids of rheumatic patients a trifle smaller than in the blood. The concentration in the aqueous humor was reported higher than that of the blood (S. R. Gifford, 1922). The concentration in the serum is perhaps a little higher than in the corpuscles (Fridericksen, 1917). Most of the salicylate in plasma is bound to nondiffusible components, presumably plasma proteins. Very little is found in the corpuscles. After oral administration of acetylsalicylic acid only unesterized salicylate is demonstrable in the plasma (P. K. Smith, Gleason *et al.*, 1946).

Free Salicylic Acid Does Not Exist in the Tissues.—Although salicylic acid may be liberated from sodium salicylate by high concentrations of carbon dioxide (Binz, 1879), the buffer action of the tissues prevents the acidity from rising to the necessary level, even in asphyxia (Hanzlik, 1921). Scott, Thoburn and Hanzlik, 1916, also failed to find free salicylic acid in the joint fluids of rheumatic patients.

Antiseptic Action.—Free salicylic acid is about equivalent to phenol and benzoic acid; its salts are scarcely antiseptic (Kolbe, 1874). The irritant effects disqualify salicylic acid as a surgical antiseptic. It has been used as a food preservative, but it is doubtful whether this should be permitted. Salicylates have a moderate antiseptic effect on the urine (Jordan, 1911), and may be used for this purpose. Saturated solution of salicylic acid has been recommended as a harmless fly poison.

Local Actions on Skin.—Application of salicylic acid in substance or strong solution produces slow and painless destruction of the epithelium. It is used as ointment, 2 to 10 per cent, in itching skin diseases (urticaria) and against pityriasis versicolor; as lotion, 1 to 2 per cent, in alopecia; as powder, 3 per cent in talc, against sweating feet; and in collodion, 10 to 20 per cent, and plasters to *soften corns and warts.* An ointment containing 3 per cent of salicylic acid and 5 per cent of benzoic acid in petrolatum (*"Whitfield's Ointment"*) is used especially against ringworm. Sulfosalicylic acid acts purely as a corrosive acid (Göpfert, 1938).

Hypersensitiveness of Skin to Salicylates.—Sauerland, 1912, found that external applications (not the systemic administration) of salicyl preparations gradually develop persistent sensitiveness, leading to eruptions after an incubation period. This involved all parts of the skin, not only that to which the salicylate had been applied. The skin was not hypersensitive to other irritants.

Local Actions.—Strong solutions of salicylic acid produce considerable irritation and superficial corrosion of *mucous membranes.* The salts are free from this objection, and the free acid is therefore little employed internally. Salicylic and acetylsalicylic acid soften the enamel of the *teeth* and should not be used in mouth washes. Acetylsalicylic acid produces some local irritation of the mouth and throat and possibly also of the stomach.

The **analgetic and antipyretic effects** are discussed in a previous section. They do not differ materially from those of acetanilid. Large doses of salicylates are safer, but have more disagreeable side actions. Acetylsalicylic acid (aspirin) is used extensively against *headache.*

Heat regulation apparently is affected quite differently *in health and in fever.* With normal men at muscular rest, 1 Gm. does not lower the temperature, but increases the heat production (CO_2 excretion about 6 per cent), with the heat dissipation practically unaffected (Barbour and

Devenis, 1919). With febrile patients, even with mild fever or when the temperature is merely unstable, the same dosage lowers the temperature to 0.8° C. below normal; and produces a great increase (38 per cent) of heat dissipation, and a slight decrease of heat production. When the effect passes off, there is compensatory decrease of heat dissipation to half the normal level (Barbour, 1919). Nitrogen excretion is primarily increased (Weber); there is often a later decrease. The oxidation of excised muscle is retarded by small concentrations.

Salicylate on Cold-Fatigue.—Immersion of the forearm in a cold bath for thirty to forty-five minutes causes a dull ache, with rapid fatigability of the muscle. Therapeutic doses of acetylsalicylic acid remove the ache and restore the normal activity, even though the cold immersion is continued. Alcohol, 17 to 33 cc. by mouth, as 33 per cent solution, acts similarly. Caffeine does not (Menschel and de Rochemont, 1926).

Time-Sense of Insects.—Ants and bees can be trained to come for feed at a certain time of the day. This is disturbed by drugs (probably by altering the speed of metabolism): ants come earlier when treated with salicylic acid or yellow phosphorus; arsenic trioxide has complex effects (Grabensberger, 1934). Bees are delayed by carbon dioxide or low temperature, unaffected by thyroid feeding and by ether (Kalmus, 1934).

Therapeutic Effects in Rheumatic Fever.—Adequate administration of salicylates controls the manifestations of this disease in a remarkable manner in nearly all typical cases. The pain and fever disappear; the local inflammation, the immobility, swelling and redness subside; the general condition of the patient is vastly improved; and the disease is under complete control in one to at most five days. These benefits last only so long as the patient is kept salicylated, and relapses occur when this is discontinued. The total duration of the disease is not shortened, as judged by the stay in the hospital (J. L. Miller, 1914), and by the sedimentation rate (Wégria and Smull, 1945). The rheumatic cardiac lesions are not relieved directly (Vulpian, 1880), although the A-V conduction may be restored to normal during salicylation (R. L. Levy and Turner, 1927). Indirectly, salicylate treatment may have an important tendency in this direction by favoring rest and avoiding the extra tax of fever, pain and insomnia.

The urine output is increased. There may be some temporary casts.

Efficiency in Related Conditions.—Salicylates are much less effective in atypical, subacute, chronic and muscular rheumatism, lumbago, and the like, although they usually have some analgetic effect (Hanzlik, 1913). In acute gout they are often quite effective (Vulpian, 1880). They are notably inefficient in scarlatinal and gonorrheal arthritis (G. Sée, 1877; Stockman, 1906). They are used in headache, neuralgias, sciatica, tabes and other similar pains, but with inconstant results. In chorea it is difficult to prove any benefits. Large doses (10 Gm. of sodium salicylate per day) have been administered over long periods in all types of *intra-ocular inflammation*, with the claim that they check or relieve the congestion (H. Gifford, 1922).

The **mechanism of antirheumatic action** is probably connected with the analgetic and antipyretic action. It is improbable that the salicylates have a germicidal effect in the tissues; nor do they improve chemical irritations and edemas (Hanzlik and Tainter, 1923). The analgetic explanation is based on the efficiency of salicylates in other painful conditions (Vulpian, 1880), and on the effect of other analgetics in rheumatic fever. Hanzlik *et al.*, 1918, found that combination of other analgetics (for instance, morphine) and antipyretics (for instance, quinine) also relieve the symptoms of acute rheumatic fever promptly and effectively. Quantitatively, however, salicylates are superior.

Salicylate prevents the *precipitation of antigen* by antibody *in vitro*, apparently by an action on the antibody (Coburn and Kapp, 1943). This is suggestive for the explanation of rheumatic fever as delayed antigen-antibody reaction. It has not been shown, however, that this salicylate effect occurs in the living body. Physiological concentrations have little effect on known *enzyme systems;* but when injected into animals, salicylate produces prompt disappearance of nearly all *liver glycogen*, with full restoration within a day (Lutwak-Mann, 1942).

Administration of salicylate to rabbits antagonizes the spreading action of the hyaluronidase of testicular extract. Sulfadiazine does not have this action (F. Guerra, 1946).

Tissue antisepsis was suggested by the large doses which are required; the lesser efficiency of other antipyretics and analgetics; the relative inefficiency of the salicylates in other forms of arthritis. Against this view speak the prompt recurrence of the symptoms if the salicylate is discontinued and the failure to prevent the cardiac infection. In rabbits, the prophylactic use of salicylate does not prevent or even influence arthritis from intravenous injection of rheumatic hemolytic streptococci (Miller, 1914; Davis, 1915); but this is not conclusive, since the etiology has not been established, and the administration is different.

Administration.—Free salicylic acid is too irritant for internal use. It may be neutralized by sodium bicarbonate, but acetylsalicylic acid is commonly used for headache, and the less toxic and cheaper sodium salicylate for the large doses required in rheumatic fever. Its mawkish taste can be greatly diminished by dilution; flavoring with peppermint or wintergreen water is not very successful.

To be effective in rheumatic fever, the amount of salicylate must be sufficient to make the patient "toxic," with tinnitus, nausea and hebetude, requiring a plasma level of at least 25 mg. per 100 cc. This may be secured by intensive oral administration of sodium salicylate, 1 to 1.5 Gm. (15 to 25 grains) in a half glass of water, every hour until relief is secured. It may then be given every four hours for several weeks, keeping the patient in bed. Sodium bicarbonate is sometimes administered in equal dosage, but it probably serves no useful purpose and tends to lower the salicylate level of the blood. Enteric capsules appear undesirable, for the salicylate is absorbed mainly from the upper intestines (R. W. Huntington, Ryan *et al.*, 1946).

Wégria and Smull, 1945, recommend 1.8 to 3.6 gm. of sodium salicylate, according to body weight, every four hours for three doses, then half this dose every four hours day and night until the sedimentation rate remains below 20 for two weeks. They find that this maintains the salicylate concentration of the plasma better than intravenous administration.

Sodium bicarbonate was originally given to dissolve free salicylic acid when this was prescribed, and was then thought to avoid acidosis, but its benefits are questionable. Alkalinization of the urine lowers the salicylate concentration in the plasma of patients by increasing its excretion. Acidification by ammonium chloride raises the blood level (F. S. Coombs *et al.*, 1944; Smull *et al.*, 1944; P. K. Smith, Gleason *et al.*, 1946). R. W. Huntington, Ryan *et al.*, 1946, found no change in the serum level with bicarbonate in daily doses up to 4 Gm.

Methyl salicylate also gives some relief when applied externally to the affected joints, but this is purely by counterirritation. The amount absorbed is not sufficient for systemic effects; nor can it make a short cut to the joints, because it is carried off by the intervening circulation. Sodium salicylate may be administered by rectum, if it is not retained by the stomach (Heyn, 1914), but the rectal absorption is poor (R. W. Huntington, Ryan *et al.*, 1946). The absorption from oral administration is so prompt that there is no real necessity for parenteral administration. Intravenous drip was advocated by Coburn, 1943, to start the treatment, but it does not materially hasten the response, and serious toxic reactions have occurred (Hench, 1946). Concentrated solutions produce sclerosis. Hypodermic injection may cause local necrosis.

The plasma salicylate level is the determining factor in the therapeutic response. A. F. Coburn, 1943, reported that at least 25 mg. per 100 cc. are necessary to obtain prompt and progressive subsidence of the inflammation. This can be secured and maintained by oral administration of 10 Gm. of sodium salicylate per day (Butt *et al.*, 1945). The oral dosage of Wégria and Smull, 1945, maintains 35 to 50 mg. per 100 cc. A single dose of 3.3 Gm. brings the level to 18 mg. per 100 cc. (R. W. Huntington *et al.*, 1945). *Intravenous drip injection* of 10 Gm. in 1000 cc. of saline or lactate-Ringer solution, during four to six hours, attains the 35 mg. level more rapidly with a minimum of salicylism. R. C. Manchester, 1946, recommends a routine of daily intravenous injections of 10 Gm. for four to ten days, followed by oral. In severe cases, 20 Gm. may be injected in eight hours. Salicylate levels of 10 to 25 mg. relieve the symptoms, but the inflammation progresses.

Salicylism.—When the dosage of salicylate is raised to the full therapeutic effect, there occurs usually a series of side actions resembling cinchonism. They consist in nausea and vomiting, ringing in the ears and deafness, vertigo and headache, mental dulness and confusion, diaphoresis, quickened pulse and increased respiration, respiratory alkalosis; rarely skin eruptions (especially pustular acne), albuminuria, impaired vision (de Schweinitz, 1895; Claiborne, 1906) and maniacal delirium, the latter especially in alcoholic patients. All these effects are usually without danger, disappearing promptly when the drug is discontinued. Abortion has sometimes occurred, but it is doubtful whether this was due to the drug or to the disease.

The *nausea and vomiting* are exceptional if sodium salicylate is used as enteric-coated tablets (Wégria and Smull, 1945); however, they do not appear to be caused by local irritation, except if free salicylic acid is given. The salicylates and esters are not especially irritant; and if fractional doses are used, the gastric phenomena set in only after some hours, about the same time as the ear and other systemic effects. They are therefore probably central. This has been confirmed by the direct method of Eggleston and Hatcher, 1915. The *ear symptoms* are perhaps connected with congestion of the auditory apparatus (Kirchner, 1881; but Haike, 1904, believes these lesions to be asphyxial artefacts). The *brain vessels* are dilated (Berezin, 1916).

The toxic symptoms follow the plasma salicylate concentration. Tinnitus usually begins with 25 mg. per cent. More serious symptoms may set in with 50 mg.; most commonly, hyperpnea with the serum CO_2 as low as 25.8 vol. per cent. A few patients have sinus tachycardia. Apathy and drowsiness are generally present; a few have hallucinations. All symptoms disappear quickly when the plasma level falls below 50 mg. per cent (Wégria and Smull, 1945). Children under intensive salicyl therapy may develop roentgenographic evidence of bronchopneumonia (D. L. Stevens and Kaplan, 1945).

The "*toxic*" *dose* was investigated by Hanzlik, 1913, in over 500 administrations. If the salicylates are administered in repeated doses of about 1 Gm., one or two hours apart, the "toxic" effects appear usually when the total dose of sodium salicylate attains between 7 and 13 Gm., 100 to 200 grains, the mean being about 12 Gm., 180 grains. Women require about four-fifths of this dose. There are no differences between sixteen and seventy-five years of age. Children have a relatively high tolerance, *i. e.*, the toxic dose is much higher than would be calculated from their age (Archambault, 1878). The dose is the same for the white and the colored race. It is not affected by the presence or nature of disease. Occasionally there are unexplained idiosyncrasies or tolerance (toxic doses as low as 20 and as high as 1300 grains). These are usually only temporary. The toxic dose of acetylsalicylic acid and methyl salicylate is about two-thirds, that of salicylsalicylic acid (MacLachlan, 1913) about one-half that of sodium salicylate. The toxic dose and effects of strontium salicylate are the same as for the sodium salt (Blankenhorn, 1916).

Decreased prothrombin level of the blood occurs early with intensive salicylate administration if the vitamin K income is scanty. The action is probably related to that of dicumarol, but salicylate is much less potent, and hemorrhagic manifestations are not likely to occur if the vitamin K income is normal. It may be advisable to protect prolonged administration with menadione.

The prothrombin level runs inversely to the salicylate level of the plasma; the lowering is insignificant until the salicylate reaches 6 mg. per cent (F. W. Clausen and Jager, 1946). The massive Coburn doses lower the level in all patients to 55 to 75 per cent, sometimes even to 20 per cent, but this usually returns to normal after some days, even if the salicylate is continued (G. C. Owen and Bradford, 1946).

Degradation of dicumarol *in vitro* leads to salicylic acid (Huebner). This has not been established *in vivo*, but Link *et al.*, 1943, showed that salicylate prolongs the prothrombin time in rats, and O.O. Meyer and Howard, 1943, reported that this occurs in the therapeutic use of sodium salicylate or acetylsalicylic acid, and can be prevented by administering menadione. This has been confirmed by others, but it has not been shown that it leads to hemorrhagic complications. These would not set in unless the prothrombin is decreased below a fifth of the normal (review, A. J. Quick, 1944; Butt *et al.*, 1945). Rats are more susceptible to the prothrombin decrease than rabbits, and these more than dogs. The effect is greatly augmented by increased metabolism, hyperthermia, thyroid administration and alcohol. It is about equal for equimolecular amounts of sodium salicylate, acetylsalicylic acid and methyl salicylate. The prothrombin level is also lowered by other antipyretic drugs, antipyrine, aminopyrine, acetanilid, acetophenetidin, cinchophen and quinine (B. B. Clark and Spitalny, 1946).

Dangerous poisoning by sodium salicylate is rare, and it is often difficult to judge whether the effects attributed to the salicylate were not really due to the disease.

The *symptoms* are described as vomiting, unconsciousness, delirium, dyspnea and deepened respiration (Quincke, 1888), fall of temperature, arrhythmia, albuminuria, paresis, collapse, asphyxial convulsions (Peterson, 1877; Weckerling, 1877; Allaire, 1879; Vinci, 1905). Sicard and Meara, 1915, attributed a case of sino-auricular block, with standstill of the entire heart, to salicylate. The *fatal dose* is stated as 5 to 12 Gm., but is exceptional; even severe cases generally end in recovery. The *autopsy* in Quincke's case showed hyperemia of the brain and its membranes, of the kidneys and lungs, and pericardial ecchymoses.

Toxic Effects in Animals.—These are similar to those in man. The respiration is deepened and labored, first quickened, then slowed to final asphyxia with convulsions. The blood pressure rises at first, then falls severely; the pulse is inconstant. The intracranial vessels are constricted (Wiechowski, 1902). There are general collapse and sometimes paralyses. The heart stops with the respiration. The autopsy shows the same congestions as in man (Koehler, 1876; Quincke, 1882). The toxicity is low, the fatal dose per vein for dogs being about 1 Gm. per kilogram. Methyl and ethyl salicylates intravenously produce pulmonary edema by injuring the capillary walls.

Acidosis.—Vuipcke called attention to the resemblance of serious salicylate poisoning, especially the hyperpnea, to diabetic coma. Langmead, 1906, and Lees, 1908, emphasized this resemblance in children, and described the occurrence of acetone even after relatively small doses of salicylates. The acetonuria is probably often due to the associated conditions of the disease rather than to the salicylate. It is prevented by administering sodium bicarbonate (H. B. Myers and Ferguson, 1929). However, the matter is not clear. There is reduction of CO_2 capacity (alkali reserve), but generally not nearly enough to account for the hyperpnea (Bowen *et al.*, 1936). The hyperpnea produces alkalosis, with significant fall of serum CO_2 (Wégria and Smull, 1945). When the dosage of sodium salicylate reaches 6 Gm., the blood reaction shifts toward alkaline, and *alkali administration* would be undesirable (K. Gebert, 1931).

Kidneys.—Salicylates may have a diuretic effect (Blanchier, 1879); or they may decrease the output of urine, partly by diaphoresis, partly by water retention. This is accompanied by evidences of renal irritation (slight albumin and casts) and diminished renal permeability (phthalein test and nonprotein nitrogen of blood). With the ordinary doses, these changes disappear rapidly, and apparently without permanent damage, on discontinuing the administration (Scott, Thoburn and Hanzlik, 1916; Ehrmann, 1907).

The albuminuria occurs in normal individuals, and is therefore due to the drug, not to the rheumatic fever (Hanzlik *et al.*). It is also produced in animals, by doses corresponding to the therapeutic. Their kidneys show histologically various grades of nephritis, especially cloudy swelling (Hanzlik and Karsner, 1917). The albuminuria, edema, and so forth, are not modified by the administration of bicarbonate (Hanzlik *et al.*, Ehrmann, 1907), contrary to the earlier claims.

Salicyl Edema.—Full therapeutic doses of salicyl diminish markedly the quantity of urine, with an almost corresponding increase of body weight. This is demonstrable about twenty to eighty hours after the start of the salicyl administration. There is no dilution of the blood hemoglobin, so that the fluid must be mainly in the tissues (Hanzlik, Scott and Reycraft, 1917).

Metabolism.—Salicylates increase the elimination of nitrogen (Laqueur, Bruenecke and Crampe, 1912), especially in the form of *uric acid;* the latter is followed by a compensatory decrease (Kumagawa, 1898; Ulrici, 1901; Schreiber and Zaudy, 1899). The increase of uric acid is probably due chiefly to lowered renal threshold for urate, as with cinchophen. The excretion of *ascorbic acid* is increased by therapeutic doses, as also the *phosphate. Creatinine* excretion is not affected (Daniels and Everson, 1936). The normal *nonprotein nitrogen* of the blood is not lowered; but when abnormally high it may be decreased. The creatine of the blood is not affected (Denis, 1915). Gaulier, 1913, claimed that the chloride excretion is diminished. There are few definite data on the respiratory metabolism (review, S. Weber, 1904). Denis and Means, 1916, found uncertain changes in the basal metabolism in man.

The gastric secretion is somewhat decreased (Klocman, 1912); but the absorption of food is not materially affected. The secretion and flow of *bile* are somewhat increased, as with cinchophen.

Continued consumption of moderate doses (0.2 to 1 Gm. per day) by healthy individuals has no significant effect on metabolism and nutrition (Wiley, 1906).

Uric Acid.—The increased elimination is due (as with cinchophen) to increased permeability of the kidneys to uric acid; for the uric acid content of the blood falls during salicyl administration, to resume its original level when the salicyl is discontinued. In man, 6 Gm. of sodium salicylate may reduce the blood uric acid to one-half or one-third. The efficiency may be greater even than with atophan (Fine and Chace, 1915; Frank and Pietrulla, 1914; Denis, 1915). The increase of urate excretion may reach 30 per cent (Denis and Means). Excised organs destroy uric acid more rapidly in the presence of salicylic acid (Stookey and Morris, 1907). Waucomont, 1911, concluded that salicylates decrease the urate and purine excretion in experimental gout. The para- and meta-isomers do not affect the uric acid excretion (Denis, 1915).

Postmortem autolysis of the liver is increased by small, and decreased by large, concentrations (Laqueur, 1912).

Cholagogue Action.—Salicylates are among the few drugs which increase the secretion of bile (Pfaff and Balch, 1897; Okeda, 1915). Other aromatic products which conjugate with sulfuric acid act similarly (Petrowa, 1912). Salicylates have been used in obstructive jaundice and biliary colic, but it is doubtful whether they are of value.

Diabetes Mellitus.—Salicylates have been credited with decreasing the output of sugar and the consumption of water (Ebstein and Mueller, 1876; von Noorden, 1912), but their efficiency is at best inconstant (Kaufmann, 1903).

Excised Heart.—The Straub frog heart and the excised rabbit heart are depressed by perfusion with sodium salicylate 0.1 to 0.2 per cent in blood; but the concentrations that could be attained in life have no effect (Fridericksen, 1917).

Skeletal muscle and nerve are practically unaffected by moderate concentrations of salicylate.

Action on Leukocytes.—Binz, 1875, found that these are paralyzed and killed, as with quinine and many other aromatic derivatives. Ikeda, 1916, observed no effect on the emigration of white cells from inflamed mesentery. In mammals, the leukocytes of the blood are said to be doubled an hour after the administration, and return to normal in two hours, but Gehrig, 1915, reported that salicylate and other antipyretics do not produce leukocytosis, as was commonly believed.

PREPARATIONS.—***Salicylic Acid,** U.S.P. (Acid. Salicylicum; Orthohydroxybenzoic Acid), occurs as white, light crystalline powder or needles; of sweetish, then acrid taste; slightly sol. in water (1:460), freely sol. in alc. (1:2.7). Dose, 0.3 to 0.6 Gm., 5 to 10 grains. ***Sodium Salicylate,** U.S.P. (Sodii Salicylas), is a white, or faint pink, amorphous or crystalline powder or scales. It is odorless or has a faint characteristic odor and a disagreeably sweet saline taste. It is soluble in water (1:1) and in alc. (1:10). Dose, 1 Gm. (0.6 to 2 Gm.), 15 grains (10 to 30 grains). Watery solutions become discolored on standing, especially if alkaline. This may be disguised by Syrup of Cinnamon, but it is advisable to dispense it as powders, to be dissolved in a tumblerful of water at the time of taking. The solution occurs rapidly. *Sodium Salicylate Tablets,* U.S.P.; usually available as 0.3 and 0.6 Gm., 5 and 10 grains. *Salicin* is sol. in water (1:28) and alc. (1:80). It has a bitter taste. It occurs in willow bark, which was used as an antipyretic in antiquity. It also occurs in poplar bark. It was introduced against rheumatic fever by Maclagan, 1876, on the basis of the fancied resemblance to malaria. It is inferior to the salicylates, because its conversion is often incomplete. Salicin is a glucoside, yielding on hydrolysis *saligenin,* $C_6H_4(OH)$-CH_2OH; this in turn is oxidized to salicylic acid (Nencki, 1870), but a part is excreted unchanged. Salicin yields 45 per cent of salicylic acid, and is therefore at most half as effective. Dose, 0.3 to 1 Gm., 5 to 15 grains, in solution or wafers.

Salicyluric Acid.—The properties of the synthetic compound of salicylic acid and amino acetic acid were studied by Hanzlik and Seidenfeld, 1930. It is stable *in vitro,* but is completely and fairly rapidly hydrolyzed into salicylate in living animals, so that it could not play a part in detoxication. Its effects are chiefly due to the liberated salicylate.

ACETYLSALICYLIC ACID (ASPIRIN)

This was introduced by Dreser, 1899. It was supposed that it would pass unchanged through the stomach, thus avoiding gastric irritation, and that the salicylic acid would be liberated in the intestine. In fact, however, it produces some gastric irritation (Roch)—indeed, large doses result in gastric ulcers; the intestinal decomposition is slow and incomplete, a part being absorbed unchanged. Acetylsalicylic acid is about one and one-fifth times as toxic as sodium salicylate in man (Hanzlik, 1913); about twice as toxic in animals (Chistoni and Lapresa). In man even small doses (0.3 to 0.65 Gm., 5 to 10 grains) occasionally produce *alarming allergic symptoms*, especially acute, local or general edema of the skin and mucous membranes, bronchial spasm, urticaria, erythema, pruritus, and so on (Graham, Morgan, Gilbert, 1911; Krause, 1914). The effects of poisonous doses in animals are similar to other salicylates (Block, 1909). These side effects make this drug inferior to sodium salicylate in rheumatic fever. It has, however, stronger analgetic and antipyretic actions, even in nonrheumatic affections, perhaps because the undecomposed acetyl compound enters the nerve cells more readily. It is used extensively in colds, influenza and other fevers; and in neuralgias, headaches, tabes, and other pains, in tablets or capsules of 0.3 Gm., 5 grains. They should be swallowed, with water, for if they dissolve in the mouth, the acidity causes some irritation and may injure the teeth, especially in gargling (D. B. Dodd, 1940). It cannot be administered dissolved by alkalis, since these decompose it. It is dangerous for persons with allergic tendencies.

The mechanism of the antipyretic action is chiefly by sweating, aided by hydremia and cutaneous vasodilatation. Hypothalamic lesions suppress the sweating, but not the lowering of temperature (F. Guerra *et al.*, 1943, 1944).

Acute Acetylsalicylic Acid Poisoning.—Suicidal attempts with 20 to 30 Gm. of the drug are fairly common in Europe. The mortality rate is about 50 per cent, death occurring sometimes with 10 Gm., but usually with 30 to 40 Gm. A patient recovered under treatment after taking nearly 65 Gm. The most prominent symptoms are intense salicylism, exophthalmos, profuse sweating and intense thirst, delirium, coma, fixed pupils, fast pulse, low blood pressure, deep abdominal breathing, severe acidosis (Oakley and Donnell, 1942). Dogs receiving 2 to 4 Gm. per Kg. by stomach tube vomit in one-fourth to one hour, then develop dyspnea, ataxia, sometimes convulsions, low blood pressure, coma, and death in eight to thirty-eight hours, preceded by brief terminal convulsions. Sodium bicarbonate prolongs life by three to eight hours, but does not prevent death (J. E. Davis, 1945). A case described by Dyke, 1935, developed hyperpnea, moderate fever, profound disturbance of metabolism, with bile, albumen and casts in the urine.

Allergy to acetylsalicylic acid is much more common than is generally supposed. It is limited almost exclusively to persons of general allergic and asthmatic tendency. Sixteen per cent of asthmatic patients reacted to 0.3 Gm. (van Leeuwen, 1928). It develops most frequently between the ages of twenty-one and fifty years. The most common reactions are asthma, urticaria and angioneurotic edema. The asthmatic attacks are likely to be severe, prolonged and resistant to treatment. They may be acutely fatal (death by laryngeal edema in a few minutes after taking 5 grains; Dysart, 1933; other cases are discussed in the J.A.M.A., 1941, *116:* 145). Other types are vasomotor rhinitis, purpura, abdominal cramps, salivation. Epinephrine is relatively ineffective (Prickman and Buchstein, 1937). Before prescribing the drug to allergically inclined patients who have not had recent experience with it, they should be tested with a minute particle on the tongue (W. W. Duke, 1933). Skin tests are not reliable, and are therefore dangerous. Desensitization by graduated doses was recommended by Widal and Vallery-Radot, 1920, but it is much simpler to employ sodium salicylate, for the allergy does not usually extend to this.

Gastric Ulcers.—Large doses of acetylsalicylic acid (150 mg. per Kg. of body weight by mouth; 300 mg. per day hypodermically) produce mucosal ulcers of the stomach in rats. They heal nearly completely in ten days. With oral administration, the corrosion is due largely to the acidity, and administration of sodium bicarbonate diminishes their severity (not calcium carbonate or gluconate, as had been reported by some). Their occurrence after hypodermic injection (which is not mitigated by bicarbonate) shows that another factor is also concerned (Barbour and Dickerson, 1938).

It is not known whether acetylsalicylic acid plays a part in the production of gastric ulcers in man. Administration of therapeutic doses definitely increases gastric acidity, and sometimes causes gastric retention (Schnedorf, Bradley and Ivy, 1936); but swallowing of two or three tablets, whole, does not produce hyperemia, edema or hemorrhage of the normal gastric mucosa (W. D. Paul, 1943).

Calcium Antagonism.—Barbour and Dickerson, 1938, could not confirm that calcium gluconate protects against gastric ulcers, as had been claimed; nor had it any effect on the acute toxic phenomena in dogs (Barbour and Porter, 1937). It could be expected to diminish the local acid action somewhat, as a buffer. Mutch, 1934, reported that calcium acetylsalicylate had less effect than the free acid in producing epiphyseal bone changes in rats. Calcium acetylsalicylate is soluble in water, but hydrolyzes with liberation of salicylic acid (H. E. Thompson and Dragstedt, 1933).

PREPARATIONS.—***Acetylsalicylic Acid,** U.S.P. (Acid. Acetylsalicylicum; Aspirin), $C_6H_4.COOH.OCOCH_3$, 1:2; a white crystalline, odorless powder of a sour taste; slightly sol. in water (1:300), freely sol. in alc. (1:5). Its incompatabilities are so numerous that it should always be prescribed in pure, solid form. It is stable in dry air, but moisture hydrolyzes it gradually to salicylic and acetic acid. It is decomposed by water, weak alkalis and acids; it is incompatible with acetanilid, antipyrine, quinine, methenamine, ammonium chloride, potassium iodide, iron salts and tannates. Dose, 0.3 to 1 Gm., 5 to 15 grains, in powders, tablets or capsules. *Acetylsalicylic Acid Tablets,* U.S.P.; usual sizes, 0.06 and 0.3 Gm. *Salicylsalicylic Acid* (Salysal, Diplosal) is tasteless and yields one-half more salicylic acid than aspirin and one-fourth more than sodium salicylate. Its toxicity in man is twice that of sodium salicylate (MacLachlan 1913). It is resistant to gastric juice, but is rapidly saponified by the duodenal secretion (Tocco 1912).

METHYL SALICYLATE

This acts somewhat more slowly, but otherwise as efficiently as sodium salicylate; the "toxic" dose is about two-thirds that of the sodium salt. The effects may be considerably delayed, suggesting slow and irregular absorption (Hanzlik and Presho, 1925). It is given internally in extemporaneous capsules, or externally as counter irritant, generally diluted with 1 to 2 parts of olive oil and painted over the affected region. *Fatal poisoning* by methyl salicylate is fairly common, especially with young children and from its use as abortifacient. An ounce is usually fatal, with convulsions, coma, gastritis and congestion of the kidneys (Pinkham, 1887).

Rosenbloom and Johnston, 1919, reported severe poisoning after 1 ounce, but with ultimate recovery. There was immediate emesis; later, severe salicylism and albuminuria, both persisting about a week. They cite the bibliography.

Ethyl salicylate is less irritant and half as toxic (Houghton, 1905). **Spirosal** is used externally, being nonirritant and easily absorbed (Impens, 1907; literature, Seifert, Nebenwirk, 1915, p. 32).

Mesotan was introduced by Floret, 1902. It is decomposed by water into salicylic acid, formaldehyde and methyl alcohol. It is used externally, but has caused dermatitis.

Methylben, U.S.P., *Methyl Parahydroxybenzoate,* Nipagen, an isomer of methylsalicylate, and **Propylben,** U.S.P., *Propylparahydroxybenzoate,* Nipasol, are used (0.05 to 0.2 per cent) as preservatives for injection solutions.

Salicylanilide ointment is used for treating ringworm of the scalp (L. Schwartz, Peck *et al.,* 1946).

PREPARATIONS.—*Methyl Salicylate,* U.S.P. (Methylis Salicylas; Oil of Gaultheria, Oil of Wintergreen, Oil of Betula, Oil of Sweet Birch), is produced synthetically or obtained from distillation from Gaultheria procumbens or from Betula lenta. It is a colorless, yellowish or reddish liquid; characteristic odor and taste of gaultheria; sparingly sol. in water, sol. in alc. in all proportions. Dose, 0.3 to 1 cc., 5 to 15 minims.

PHENYL SALICYLATE (SALOL)

This was introduced by Nencki, 1886. Being insoluble, it passes the stomach practically unchanged; but is gradually decomposed into its components, 40 per cent of phenol and 60 per cent of salicylic acid, in the intestine, by the saponifying action of the alkali, pancreatic lipase and putrefactive bacteria. This avoids the taste of the components and the local gastric action; and since the decomposition is gradual, the local intestinal action is less violent and the toxicity is materially lessened. This "Nencki's salol principle" has been extensively applied in the form of other phenolic esters, *f. i.,* guaiacol carbonate, to mitigate the taste, local actions and toxicity of other active phenols or acids.

Phenyl salicylate (and methyl salicylate) are used in "sunburn ointments" to protect the skin against ultraviolet radiation. Absorption, if any, is insignificant (Luckiesh *et al.,* 1946).

Therapeutic Uses.—Salol did not fulfill expectations. The toxicity of the phenol limits the dosage, and its absorption is so slow that it is practically inferior to the other salicyl compounds in rheumatism or as urinary antiseptic (Sollmann, 1908). The phenol component was thought to be valuable as intestinal antiseptic, especially infantile diarrhea; but the decomposition is so slow and the absorption of the phenol so rapid that effective quantities could not come into action. The clinical and experimental evidence is not conclusive (Harris, 1912). As a wound antiseptic it would be valueless because it is not decomposed by wound secretions and only slowly by bacteria. Its use in tooth powders has caused eczema of the lips (Hugenschmidt, 1907). Perhaps its main value is as a coating for "enteric pills," *i. e.,* pill masses which are intended to pass the stomach unchanged (*f. i.,* ipecac in dysentery). It must be remembered that a coating sufficiently heavy to be effective introduces large doses of salol.

Decomposition and Antiseptic Action.—Salol is decomposed to a slight extent in the mouth and stomach by bacteria (Lesnik, 1887). It is split by human milk, so that its administration to nursing infants may cause gastric irritation (Usener, 1912). Its saponification by pancreatic ferments and alkalis is slow and incomplete, insufficient to prevent putrefaction even in test tube experiments; it is inferior to sodium salicylate or bismuth subnitrate (Sollmann, 1908). A part escapes decomposition in the intestines and passes unchanged into the feces—5 to 8 per cent in the experiments of Bondzynski and Humnicki, 1909; but doubtless often much more. If given in capsules, it may be found in the feces as crystals, "*salol calculi*" (Brossard, 1897), formed by the partial fusion and recrystallization of the salol (C. R. Marshall, 1897). It should therefore be administered subdivided as an emulsion or with indifferent powders.

Preparations.—*Phenyl Salicylate* (Phenylis Salicylas; Salol) is a white, crystalline powder melting at about 42° C., of a faint aromatic odor and taste; slightly sol. in water (1:6670); very sol. in alc. and fixed and vol. oils. Dose, 0.3 Gm., 5 grains; maximum dose, 2 Gm., 30 grains; in powders, generally with bismuth. Externally, as 5 per cent ointment.

BENZOIC ACID AND BENZOATES

Benzoic acid, $C_6H_5CO_2H$, occurs in balsams (Benzoin, Tolu, and so forth), in cranberries and in other vegetables; and in the decomposed urine of herbivora. It is now prepared synthetically. It is a fairly strong antiseptic of about the same rank as phenol; the salts are somewhat less efficient. The free acid in concentrations above 0.1 per cent produces moderate local irritation; the salts are not irritant. The systemic toxicity is low, even large doses producing mainly digestive derangement, sometimes with further effects, resembling those of salicylates. There is also a similar, but weaker, therapeutic action in rheumatic fever. Fatalities are unknown. Benzoic acid combines in the kidneys with glycocoll to form the inactive hippuric acid. This is used as a test of liver function. It also conjugates with glycuronic acid (review, L. Young, 1939). The low toxicity and the absence of odor or marked taste have led to the use of benzoates for the *preservation of foods*, especially fruits and vegetable products. Sodium benzoate is generally employed for this purpose in the concentration of 0.1 per cent; in acid foods, especially fruits, most of the benzoic acid would be liberated. This concentration suffices to restrain bacterial growth considerably, but may not prevent it completely. The *local actions* of benzoic acid are analogous to those of salicylic acid, and it is used similarly in dermatology, as a mild antiseptic stimulant and irritant, as an ingredient of Whitfield's ointment, and in the form of benzoin to promote the healing of small wounds, chapped hands, and the like.

Antiseptic Efficiency.—Buchholz, 1875, found the free acid germicidal in 0.4 per cent, and antiseptic in 0.1 per cent. Salkowski, 1899, found that 0.25 per cent kept meat sterile for five months; with 0.1 per cent there were only a few colonies. Sodium benzoate in neutral media inhibits growth in 0.3 to 0.5 per cent (Th. Smith).

Action on Digestive Ferments.—In test tubes, benzoic acid up to 0.1 per cent does not interfere markedly, but higher concentrations are detrimental, especially to pepsin (Leffmann, 1899). Peptic digestion proceeds fairly rapidly, however, even in a saturated solution (Dakin). These actions have no practical importance (Long, 1912)

Hippuric Acid Synthesis.—Benzoic acid and its homologs (cinnamic acid, quinic acid, and so forth), combine in the body with amino-acetic acid (glycocoll) to form hippuric acid. In man, benzoic acid up to 10 Gm. per day is excreted almost quantitatively as hippuric acid (Dakin, 1910) (85 to 90 per cent within five or six hours; H. B. Lewis, 1914). With large doses (25 Gm., Lewinski) a part escapes synthesis. Injected hippuric acid is excreted rapidly, *i. e.*, within nine hours (Raiziss, Raiziss and Ringer, 1914). The normal hippuric acid (averaging 0.7 Gm. per day in man) arises in this matter from the benzoic acid occurring naturally in vegetable foods; and from its homologs which are formed in protein putrefaction in the intestines (Baumann, 1886). Meissner and Shepard, 1866, showed that the synthesis of hippuric acid occurs in the *kidneys*. Bunge and Schmiedeberg, 1877, demonstrated the process in excised kidneys, and believed that this is the only organ concerned in dogs. Considerable hippuric acid is formed, however, in nephrectomized dogs (Kingsbury and Bell, 1915). In herbivorous animals, the synthesis takes place partly in other organs (Salomon, 1877), in the small intestines and liver (Jaarsveld and Stokvis, 1879). The *liver* also participates in dogs, for the hippuric acid is diminished by the injection of hydrazine, which induces fatty degeneration of the liver, but is supposed to leave the kidneys untouched (Lackner *et al.*, 1918). Chickens do not form hippuric acid (Yoshikawa, 1911).

Hippuric Test of Liver Function.—The conversion of benzoic into hippuric acid is incomplete if the supply of amino-acetic acid is inadequate, since this is formed in the liver, its deficiency indicates derangement of liver function. The test consists in the slow intravenous injection of 1.77 Gm. of sodium benzoate in 20 cc. of water (A. J. Quick, 1939). The hippurate output has been reported below normal in acute and epidemic hepatitis, obstructive jaundice, hepatic cirrhosis, hepatic carcinoma (Rennie, 1932); in schizophrenic catatonia (Quastel and Wales, 1940); also after anesthesia, general and spinal (Boyce and McFetridge, 1938). The latter, however, may be due to renal deficiency (Mann). The *conjugation of substituted benzoic acids* was studied by Quick and Cooper, 1932. *Diphenylene oxide* increases hippuric acid excretion, indicating that it is hydrolyzed with the formation of benzoic acid (Christomanos, 1929).

The **actions of sodium hippurate** resemble those of benzoate and salicylate, but are more feeble. The absorption of hippuric acid from the digestive tract is slower than with benzoic acid; its urinary excretion is more rapid. Both acids inhibit the uptake of oxygen by minced or sliced tissue (Griffith, 1938).

Clinical studies of moderate doses of benzoate are important in view of the use of benzoates for the preservation of food. Chittenden, Long and Herter, 1911 (Report 88, U. S. Dept. Agr.), could not demonstrate any effects on healthy individuals if larger quantities than are likely to be used in foods, 0.5 Gm. per day, were continued for weeks. Even 4 Gm. were not generally injurious. Others found no untoward effects with 12

Gms. daily over long periods (A. J. Quick, 1944). Wiley *et al.*, 1908, claimed some digestive disturbance by 1 to 2.5 Gm. in capsules, but the results were not striking, and their significance is doubtful (K. B. Lehmann, 1911). Excessive concentrations (above 0.1 per cent) of the free acid, consumed too liberally (as in cider or fruit juices) probably cause more pronounced gastro-intestinal irritation (Lucas, 1910), but not albuminuria (Herter, 1910). These concentrations have a noticeable taste which serve as a warning. There is no reason to assume that the benzoate has a cumulative action, since it is promptly excreted as hippuric acid; nor is there any evidence that the formation of this acid is in any way detrimental.

Permissibility of Benzoated Foods.—These investigations justify the conclusion that healthy individuals may safely consume reasonable quantities of benzoated foods (0.5 Gm. of benzoate per day, in concentration of 0.1 per cent), if these foods are not otherwise spoiled or unhealthful. Benzoate is probably the least harmful of food preservatives, and where these are needed, its use appears permissible, provided that its presence is stated so that it may be avoided by patients with gastro-intestinal or renal diseases to whom it could be harmful.

Possible Objections.—The evidence in favor of benzoates is really negative, viz., that no deleterious effects have been proved. Such negative evidence is always open to the objection that the methods of investigation may not be sufficiently delicate or comprehensive, or otherwise are not adapted to reveal the possible deleterious effects. More serious probably is the objection that the investigations were confined almost exclusively to healthy individuals. It is conceivable that irritant actions too feeble to influence normal organs might become deleterious to these organs, especially the gastro-intestinal tract or kidneys, if these are already diseased, or when the general resistance is lowered. Herter, 1910, advised against the free use of benzoates in dyspepsias. There is also evidence that the formation of hippuric acid, which is probably in part responsible for the harmlessness of benzoic acid, is interfered with in at least some types of kidney diseases.

Effects of Large Doses.—Sodium benzoate is tolerated without serious symptoms even in much larger doses, at least up to 60 Gm. per day (Jaksch, 1897). Such doses were formerly used in therapeutics. There are generally symptoms resembling those of salicylates (Rost, Franz and Heitzel, 1913). The dose required to elicit these symptoms varies greatly: nausea and vomiting were obtained in some cases with 6 to 8 Gm. (Meissner and Shepard, 1866); in others, 25 Gm. had no effect. The urine sometimes contains reducing substances, presumably glycuronic acid, especially if large doses (25 Gm.) are taken (Lewinski). The *toxic effects on animals* are analogous to those of phenol: gastric irritation, vomiting, dyspnea, decrease of reflexes, narcosis, sometimes convulsions (Kobert and Schulte, 1880). Dogs tolerate 1.7 Gm. per kilogram by vein without danger. This produces short vagus stimulation and prolonged rise of blood pressure (Naumann 1879). No effects *on the growth of rats* were observed with a diet containing 2½ per cent of the salt; but with 3 per cent, a third of the rats died (Griffith 1929).

The **internal therapeutic uses** are not important. The slightly irritant action of free benzoic acid has been used in *bronchitis* to promote expectoration, especially when the secretion is thin and abundant. Slow intravenous injection of sodium benzoate 5 to 10 cc. of 25 per cent solution, once or twice daily for two weeks, has been tried against *tuberculous cough* (Quaranta, 1936) and *pulmonary suppuration* (Goldkorn, 1937). These would be expected to produce acid flocculation, and would therefore act by colloidoclastic reaction rather than as benzoates. It has been claimed that hypodermic as well as intravenous injection of large doses of benzoate (and of iodobenzoates and iodosobenzoates) inhibit *mustard oil chemosis* in rabbits (Bernheim *et al.*, 1932), but this is notoriously difficult to judge. Benzoate could be used in *arthritis* as substitute for salicylates; but it is not so effective, and has no advantage. Benzoate has been used in *cystitis* as diuretic and to render the urine acid and antiseptic. The diuresis is uncertain, and the antiseptic action on the urine is weaker than that of salicylate (Sollmann, 1908). Benzoate was formerly employed to eliminate *uric acid* (Ure, 1841), but it is less effective than salicylate. Large doses (8 Gm. per day, in man) increase the elimination of urates in the urine, and decrease the urate content of the blood. The creatinine of the blood is not lowered (Denis, 1915). H. B. Lewis and Karr, 1916, observed a marked decrease in uric acid excretion during the period of maximal hippurate excretion, after 7 to 8 Gm. of benzoate. This effect is not produced by administering hippuric acid directly. Creatinine excretion was not affected by the benzoate.

PREPARATIONS.—*Benzoic Acid,* U.S.P. (Acid. Benzoicum), C_6H_5COOH; white crystalline scales or needles; slightly sol. in water (1:275), freely sol. in alc. *Sodium Benzoate,* U.S.P., is freely sol. in water (1:2). Dose, 1 Gm., 15 grains.

CINNAMIC ACID

Not much is known about the pharmacologic actions of cinnamic acid, $C_6H_5.CH:CH.COOH$, which occurs in Balsam of Peru. Erdmann and Marschand, 1842, showed that it is largely converted into benzoic and hippuric acids. After administration of 6 Gm. to man, 4 Gm. of hippuric acid are excreted in the urine within four hours, the same as with equivalent doses of benzoic acid (I. Snapper, Yu and Chiang, 1940). It has no effect on urate metabolism (Denis, 1915). Intravenous injection into rabbits first decreases, then increases, the blood platelets. This is followed by mild leukocytosis, especially of the lymphocytes (Claeson, 1929). Sodium cinnamate (*hetol*) was used intravenously by Landerer against tuberculosis, to cicatrize the foci by localized inflammatory reaction, but the results were disappointing. Cinnamic acid was proposed as a food preservative, but the German commission decided that while its toxicity is low, its harmlessness had not yet been sufficiently demonstrated to make its use permissible (Heffter and Rubner, 1914).

QUINIC ACID

This is hexahydro-tetraoxy-benzoic acid, $C_6H_7(OH)_4$·COOH.H_2O. It occurs in cinchona bark, coffee and many other plants. In man (also in rabbits, not in dogs; Stadelmann, 1879) it is largely transformed into benzoic acid and excreted as hippuric acid (Lautemann, 1863). Weiss, 1899, claimed that it lessened the formation of uric acid and had a beneficial effect upon gout. Decreased urate elimination was also claimed by Forester, 1900. Several observers reported clinical benefits, and various compounds were placed on the market (*urosin, sidonal, chinotropin*, and so on). Further observations showed the effects to be negative. Denis, 1915, found neither increase of urate elimination nor decrease of the urate content of the blood.

CINCHOPHEN (PHENYLCINCHONINIC ACID)

This substance, *phenyl-quinoline-carboxylic acid*, was introduced under the name of *atophan*. Its actions resemble those of the salicylates. It is about equally effective as antipyretic; it is often more effective as analgetic, particularly in chronic arthritis, and it provokes a greater excretion of uric acid, by a direct action on the kidneys. The minor side actions are usually smaller than with the salicylates. It was introduced by Nicolaier and Dohrn, 1908, to eliminate uric acid in gout, but the relief seems to be due almost entirely to its general analgetic effect. Occasionally, severe and fatal hepatitis develops, sometimes after a few therapeutic doses. The drug should therefore be avoided, or used only under close supervision, and stopped with the first indication of gastro-intestinal disturbance, itching, skin rashes or jaundice. Cinchophen and neocinchophen are not suitable for self-medication, and should be used by physicians only if the risks appear fully justified by the expected benefits. Most physicians do not consider them indispensable. They should not be used on persons with allergic tendencies (Report, Council on Pharmacy and Chemistry, 1941). The precipitation of uric acid from the urine furnishes a special contraindication in urate calculism. Cinchophen is but slightly soluble in water; but its acidity produces some irritation in the throat and stomach. *Neocinchophen* (tolysin), in which the carboxyl hydrogen is replaced by an ethyl group, and a hydrogen in the quinoline by a methyl group, lacks this acid action, and is nonirritant. Its limited solubility hinders the absorption of acutely toxic doses, but is sufficient for the therapeutic effects. Other *related compounds* were investigated by Impens, 1912, and the relation of their chemical configuration to the diuretic action by Kaku and Yamaguchi, 1929.

Fate of Neocinchophen.—In *man*, oral doses of 6.6 Gm. are absorbed practically completely and without saponification. The greater part is destroyed in the organism. In *rabbits*, a small part is excreted as dioxymethyl cinchophen (O. Fuerth and Kuh, 1930). *Cinchophen* is oxidized in the benzene nucleus (Dohrn, 1912).

Administration as Analgetic and Antipyretic.—The usual dosage of cinchophen is 0.5 to 1 Gm. suspended in water, four times per day. With larger doses, it is advisable to render the urine alkaline for one or two days by the administration of 15 Gm. of sodium bicarbonate, acetate or citrate, to prevent precipitation of urates. Neocinchophen may be given as tablets in the same dosage. The cinchophens are fairly efficient against neuralgic and rheumatic pain, and sometimes even against sciatica (McLester, 1913); but like most analgetics, they tend to become less effective with continued use. Its chief use is in gouty arthritis (Hench, 1936).

The antipyretic action was studied on animals by Barbour and Lozinsky, 1923.

Acute Rheumatic Fever.—Neocinchophen is generally as efficient as the salicylates. Partial relief has occurred with 7 to 8 Gm.; complete relief of fever, pain and swelling generally requires 10 to 16 Gm. The patients do not show the nausea and other symptoms of salicylism, nor does there appear to be any renal irritation with therapeutic doses (Hanzlik *et al.*, 1921; Barbour, Lozinsky and Clements, 1923).

Anticonvulsant Action.—In rabbits, cinchophen diminishes or prevents convulsions by minimal effective doses of metrazol (L. J. Pollock *et al.*, 1942).

Antiphlogistic Action.—It has been claimed that the administration of cinchophen diminishes experimental inflammatory edema in croton oil dermatitis and mustard oil chemosis (Starkenstein, 1919), but this holds true only of doses that produce collapse (Fuerst, 1925). Doses corresponding to the therapeutic toxicity do not improve chemosis or phosgene pulmonary edema (Laqueur and Magnus, 1921), or paraphenylene-diamine anasarca (Hanzlik and Tainter, 1923). Cinchophen inhibits completely the emigration of *leukocytes* in the inflamed frog's mesentery, and exhibits in this respect a potentiated synergism with quinine (Ikeda, 1916).

Use in Gout.—The mobilization of uric acid was supposed to be useful in gout by removing it from the blood and by dissolving the tophi. The uric acid and the nonprotein nitrogen of the blood are in fact lowered by it, the urate especially in gout, since the increase of renal permeability by cinchophen would offset the impermeability characteristic of gout (Folin *et al.*, 1924). Feulgen, 1912, claimed that the tophi are actually decreased in some cases. Clinically, however, cinchophen is much less efficient in chronic gout than in the acute attacks and in nonuratic joint affections. This makes it probable that cinchophen acts as an analgetic similarly to salicyl. In agreement with this, Klemperer, 1913, found derivatives which lack the uratic action equally efficient clinically.

Effect on Uric Acid Elimination.—The excretion of uric acid is greatly increased, sometimes more than doubled, by therapeutic doses, even on a purine-free diet. The increased excretion begins within an hour (maximum in three hours) and lasts only as long as the drug is continued; and it is then followed by a compensatory decrease (Haskins, 1913). The effect is attributed to increased permeability of the kidneys to urates. Several other explanations were proposed and abandoned (see Sixth edition of this Manual, page 636).

With continued administration, the uric acid returns to normal after one or two days, unless the diet contains purines. In that case, the decrease may be postponed till the fifth day (Grabfield and Pratt, 1922). The uric acid of the blood is diminished by the increased excretion (Folin and Lyman, 1913), but soon reaches an irreducible minimum; there is no further lowering even if the administration is continued forty-five days. When the administration is stopped, the initial concentration is restored within two to four days (Fine and Chace, 1914; Frank and Pietrulla, 1914). The response varies rather widely. When the renal cells have been severely injured, in the late stages of interstitial nephritis, cinchophen has little effect on the uric acid excretion (Fine and Chace, 1915). The concentration of urates in the urine may become so great that they are precipitated before the urine is voided; cinchophen apparently also decreases the solubility of urates in urine (Haskins, 1916). The urine is of a dark color, due to urochrome (Skorczewski, 1912). In other respects, its composition and quantity are not notably changed. The leukocytes of the blood are also unaltered.

Other Changes in Urine.—Cinchophen and neocinchophen act similarly to salicylate. They tend in general to increase the renal excretion of solids, most markedly that of uric acid, but also urea and chlorides, if the level of these in the blood is even slightly higher than normal (V. C. Myers and Killian, 1921; A. F. Chace, Myers and Killian, 1921). Cinchophen is much less reliable than salicylate to produce proteinuria and casts (Fine and Chace, 1915). McLester, 1913, reported an increase in the quantity of urine and of total nitrogen. Eisner, 1915, found the excretion of chloride and total nitrogen as often diminished. Renal function tests gave inconstant results.

The creatine content of the blood is not decreased (Denis, 1915).

Bile Secretion.—Cinchophen is one of the most effective choleretic agents. In dogs with ligated cystic duct, it increased the bile flow to five times in the first hour, and even after five hours it was still three times the normal. The output of bile pigments is also increased, but the bile acids and cholesterol are decreased (Chabrol and Maximin, 1929). A considerable part of the injected cinchophen was recovered from the bile (20 per cent in five hours, 55 per cent in a day; W. B. Bradley and Ivy, 1940). The biliary excretion of cinchophen is hastened by bile salts (Annegers *et al.*, 1943).

Biliary Eosin Excretion.—Brugsch and Horsters showed that some acid dyes, notably eosin, are excreted exclusively by the bile. K. Franke, 1930, found that small doses of cinchophen increase this eosin excretion by two or three times, without increasing the volume of the bile; large doses, which increase the bile volume, decreased the eosin excretion. Decholin increased both the volume and the eosin output. Neocinchophen hastens the excretion of sodium tetraiod-phenolphthalein by the bile (R. G. Spurling and Hartman, 1926).

Minor side actions are frequent. They depend in part on the acidity of the cinchophen, resulting in digestive irritation, epigastric distress, acid eructation, complete anorexia and diarrhea. If due solely to the acidity, these may be avoided by administering sodium bicarbonate with the cinchophen; however, digestive disturbances may be the initial symptoms of toxicosis. Large doses may produce symptoms analogous to those of salicylism, including emesis by central action. More specific effects are witnessed occasionally, especially skin rashes, puerperal, scarlatinal, urticarial or vesicular (C. L. Short and Bauer, 1933; Sutton, 1936). Cardiac distress and dizziness may occur as with other antipyretics (Loening, 1913). In cystitis it may produce vesical pain and hematuria.

Clinical Cinchophen Toxicosis.—For fifteen years after the introduction of cinchophen in 1908, only the minor side effects had been reported, and the drug was considered practically nontoxic. In 1923, Worster-Drought described the occurrence of jaundice after its use, and this was brought to general attention especially by Klinkert, 1926, and sporadic cases have continued to accumulate. From the literature of 1922 to 1931, von Oettingen has collected thirty fatal cases of hepatitis, and forty-five serious intoxications from cinchophen or its compounds. Their occurrence is capricious. Most patients do not show any bad effects, although they may have taken large doses day after day, for years (Hench, 1936). Others, with the same history, may suddenly develop the hepatitis; in others it occurs after a few clinical doses, such as 3 Gm. for two days. Most cases have a history of 0.5 Gm., three or four times a day, for varying periods, usually a week or longer. It seems to be especially common when the administration is resumed after an interval (Sugg, 1938).

The *symptoms* start with gastro-intestinal disturbance, nausea and vomiting, marked hepatic tenderness or pain, icterus; they progress to terminal stupor and death in coma, usually within one or two weeks after the beginning of the icterus. About half of the jaundiced cases end in death, notwithstanding prompt withdrawal (Palmer and Woodall, 1936). The *autopsy* generally reveals fatty yellow atrophy of the liver, often with some degeneration of the myocardium and kidneys. In nonfatal cases, *recovery* is slow.

That toxicosis occurs in a relatively small proportion of patients exposed to cinchophen signifies that there must be a *hypersusceptibility*, and it was suggested that this may consist in an incipient hepatitis; however, this has not yet been confirmed, and it is highly toxic to many persons who do not have a history of hepatic impairment. It is probable that large or repeated doses always cause some hepatic damage, but moderate degrees of this are so well repaired that they escape clinical recognition (MacBryde, 1940). It is apparently not an ordinary allergy; nor is acidosis an essential factor. The insoluble esters, because of their limited solubility and absorption, may be less toxic. Biliary and hepatic diseases should be definite *contraindications* to the use of cinchophen.

Precautions.—Cinchophen (and neocinchophen) administration always entails risk of hepatitis; even tried-out tolerance does not assure safety. If it is used, intermissions of six to eight days should be alternated with three or four days of administration. The liver should be palpated daily, and the urobilinogen elimination should be watched.

After the symptoms have developed, *treatment* is not promising. It has been advocated to increase the glycogen store, by a carbohydrate diet and by the injection of glucose and insulin. Calcium therapy has also been suggested, but its justification is doubtful.

Chronic Toxicosis in Animals.—Oral administration of cinchophen to dogs, rats and guinea pigs, when continued over several weeks with doses considerably larger than would correspond to the therapeutic dose, but which do not produce acute effects, results constantly in hepatitis, progressing to fatal yellow atrophy. Degenerative changes occur also in the kidneys and myocardium (Rici, 1932; Van Wagoner and Churchill, 1932; Barbour and Fisk, 1933; K. K. Chen, 1936). Somewhat smaller doses lower the resistance to other hepatic poisons. The toxicity is greater with diets low in carbohydrates, and if the animals are in poor condition (Radavin and Lederer, 1933). Doses of about double the human therapeutic level produce varying degrees of effects in different dogs (Annegers *et al.*, 1943).

Gastric and duodenal ulcers can be produced in dogs by large doses of cinchophen, and several clinical cases have been reported (Bloch and Rosenberg, 1932). The canine ulcers are similar to spontaneous peptic ulcers in man. They start with acute gastritis, beginning within a day after the administration starts, with diffuse cell infiltration or small focal abscesses (Simonds, 1938).

Acute Toxic Actions on Animals.—Large doses produce convulsions, paralysis and coma. Intravenous injection, in rabbits, is followed by stimulation of the vagus and vasomotor centers; these, as also the respiratory center, are finally depressed. The pupils are constricted, even after atropine. Cinchophen is said to prevent asphyxial and puncture glycosuria (Starkenstein and Wiechowski, 1914). The fatal dose of cinchophen with oral administration to dogs is about 1.25 Gm. per Kg., about twice as high as that of acetylsalicylic acid. Neocinchophen is not toxic in any dose, as only a limited quantity is absorbed (Barbour and Lo insky, 1923).

Barbour and Winter, 1929, claimed that the *magnesium salt of cinchophen* is less toxic than the sodium salt, and at the same time more effectively antipyretic.

PREPARATIONS.—*Cinchophen* (Phenylcinchoninic Acid; Atophan) and *Neocinchophen*, U.S.P. (Novatophan, Tolysin), are nearly insol. in water, sol. in alkalis. Dose, 0.3 to 1 Gm., 5 to 15 grains. *Neocinchophen Tablets*, U.S.P.; usual sizes, 0.3 and 0.5 Gm.

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SULFONAMIDE COMPOUNDS

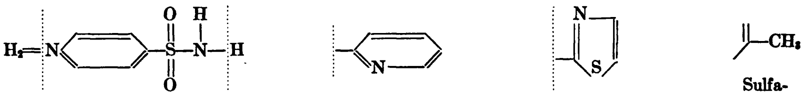
Sulfanilamide, the amide of sulfanilic acid, and its derivatives, colloquially called "sulfa drugs," check the growth of certain bacteria and other micro-organisms in the blood and tissues, producing bacteriostasis and thus giving better opportunity to the natural defense organisms to combat infections, local and systemic. The mechanism of this antibacterial chemotherapy is not directly bactericidal, but apparently involves interference with processes that are important for the metabolism and multiplication of the bacteria. This opened up a new concept of chemotherapy, that of the "*antibiotic*" action, differing rather fundamentally from that of Ehrlich, which aimed at direct death of the invading organisms. The term "*chemotherapy*" is still used somewhat artificially to designate the treatment of infections by chemical means in the living body.

Sulfanilamide was originally reported as acting specifically on infections caused by beta hemolytic streptococci, but it affects several genera of bacteria, especially the gram-negative meningococci, gonococci, pneumococci, certain viruses and, rather feebly, a few protozoa. The effect develops gradually during some forty-eight hours, and must be maintained for a week or two, by continuing the administration, to prevent recurrence. Various toxic effects may complicate the administration and may prove alarming, but are rarely fatal. The administration requires daily supervision by the physician, and it is desirable that the blood concentration of the agent should be frequently checked (by the method of Bratton and Marshall, 1939, J. Biol. Chem., *128*:537), to maintain a level adequate for therapeutic effects without incurring unnecessary danger. Derivatives show quantitative predilections for specific infections, and differ in toxic effects.

Chemical Structure.—Sulfanilamide, para-aminobenzene sulfonamide, was shown by Fourneau to be the active part of the original "prontosil." It permits innumerable substitutions in either of two situations: (1) the amino group, as illustrated by prontosil and neoprontosil, which probably act by conversion into sulfanilamide; and (2) in the sulfonamide group, such as sulfapyridine and sulfathiazole, which are not decomposed in the body and therefore act as such.

Nearly all the active derivatives contain a nitro or amino group in para position to the sulfur. The action is retained if the sulfur is replaced by As, C, P, Se, or Te, and by paranitrobenzoic acid (S. M. Rosenthal, 1939).

SULFONAMIDE SUBSTITUTIONS



Sulfanilamide

Sulfapyridine

Sulfathiazole

Sulfa-methyl-thiazole

The application of the name "prontosil" to a number of substances has caused serious confusion in the literature of the subject. "Prontylin" is sulfanilamide.

Historical.—Sulfonamide chemotherapy started with the discovery of Domagk, 1935, that azocompounds of the sulfanilamide group protect mice against infection with virulent hemolytic streptococci, and "*prontosil*" was introduced as having an especially favorable therapeutic index. The results were confirmed by Colebrook and Kenny, 1936, and applied clinically, especially to puerperal fever. Trefouel *et al.*, 1935, in France, found that other azo dyes derived from para-amidobenzene combat streptococcal infections and suggested that this is due to reduction to sulfanilamide in the organism. Buttle *et al.*, 1936, in England, showed on mice that the therapeutic potency of *sulfanilamide* (which was first prepared by Gelmo, 1908) equals that of prontosil and is less toxic. Various investigators have experimented with many derivatives, but most of these did not appear to have any real advantage, and many had a less favorable ratio of therapeutic and toxic potency, so that only a few were introduced clinically.

Fate.—Most sulfonamide drugs are absorbed more or less readily, from the gastrointestinal tract, the speed varying with the compound. They are distributed readily through all tissues and excreted chiefly by the urine, partly free, partly acetylated, the degree of conjugation varying with the compound and differing with animal species. A part is destroyed, and a small amount is temporarily fixed in the liver and kidneys. The concentration in blood, which determines the therapeutic and toxic actions, must be kept fairly constant day and night (E. K. Marshall *et al.*, 1937). Because of the variables it cannot be predicted with sufficient accuracy from the dosage, but must be checked by chemical tests. The acetylated compounds are generally less soluble and tend to form urinary concretions which may block the urinary tubules and produce mechanical irritation.

The absorption of *sulfapyridine* is slower and more variable than that of sulfanilamide; the proportion of the conjugated form is higher; and the excretion is more sustained (Marshall and Litchfield, 1939; Long, 1939). *Sulfathiazole* resembles sulfanilamide (Long *et al.*, 1940), but is absorbed more rapidly. The absorption of the sodium salts of sulfapyridine and sulfathiazole from the alimentary tract in man and monkeys is faster than that of the free substance, and is further hastened by simultaneous administration of alkalis, sodium bicarbonate or magnesium oxide (Ratish, Davidson and Bullowa, 1940; Barlow and Climenko, 1941). Sulfaguanidine and succinylsulfathiazole are absorbed slowly (E. K. Marshall *et al.*, 1941).

Absorption after Oral Administration.—Sulfanilamide is completely absorbed, usually within four hours. The absorption of sulfapyridine is less complete, averaging about 50 per cent, but it ranges from nothing to nearly complete. The difference is largely explained by the greater solubility of sulfanilamide (Long, 1939). Sulfathiazole and sulfamerazine average about 85 per cent absorption, sulfadiazine about 70 per cent.

Acetylation is a disadvantage, as it decreases the therapeutic efficiency, increases the toxicity and tends to force urinary concretions. The percentage of acetylation of the important compounds during their clinical administration averages about as follows (Chemotherapy Exhibit, A.M.A., 1944): in the *blood*, sulfapyridine, 65; succinylsulfathiazole, 50; sulfapyrazine, 30; sulfaguanidine, 25; sulfathiazole, 20; sulfanilamide, sulfadiazine, sulfamerazine, 15. In the *urine*, sulfapyrazine and sulfapyridine, 70; succinylsulfathiazole, 55; sulfamerazine, 45; sulfanilamide, 40; sulfadiazine, 30; sulfaguanidine, 25; sulfathiazole, 20 (Reinhold *et al.*, 1940; Sadusk *et al.*, 1942). Sulfanilamide is acetylated almost completely in rabbits, almost none in dogs (E. K. Marshall *et al.* 1937).

The *site of acetylation* of sulfanilamide is exclusively in the liver for rabbits and rats (J. S. Harris and Klein, 1938); but acetylation is not a valid test of liver function (Carryer and Swanson, 1942). In cats, the spleen also participates (Van Winkle and Cutting, 1940). Sulfanilamide acetylation in the rat is increased by pyruvate and to a less degree by acetoin. It is diminished materially by acetate, and also by deficiency of thiamine and riboflavin (G. J. Martin and Rennebaum, 1943). Homogenized *liver pulp* acetylates considerable sulfanilamide, sulfathiazole and paraminobenzoic acid, if aerated; very little if air is excluded. Addition of acetate doubles the amount; acetoacetate and pyruvate increase to a less degree (F. Lipmann, 1945). Quinine lowers the ratio of free to conjugated sulfapyridine in the urine by nearly half, quinacrine by less than an eleventh (Harned and Cole, 1942).

Sulfanilamide is used for determining the acetylating capacity of the organism. This is increased by administration of acetate, pyruvate, lactate, glucose, alcohol. It is also increased by giving thiouracil, decreased by thyroid and in hyperthyroidism (review, J. Fraenkel-Conrad and Greenberg, 1946).

The *blood concentration* varies widely for different patients with the same dosage per Kg. of body weight, even with sulfanilamide and sulfathiazole, and more so with sulfapyridine; the latter, however, runs a more even course, since it falls more slowly between administrations (Long and Feinstone, 1938). The therapeutic dosage is aimed at maintaining the blood concentration of sulfanilamide at 10 mg. per 100 cc., with sulfapyridine at 4 to 6 mg. per 100 cc. of the nonconjugated, as determined by the method of Marshall and Litchfield, 1938. With a single oral dose of 5 Gm. of *sulfapyridine*, the peak concentration of 2 to 4 mg. per 100 cc. is attained in six to twelve hours; with the same dose of sodium sulfapyridine, orally, 4 to 6 mg. is attained in four to six hours (Ratish *et al.*, 1940). *Sulfathiazole* gives practically the same concentration of unconjugated substance as equal doses of sulfapyridine, but the latter gives a higher concentration of conjugated (Barlow and Climenko, 1941). The peak is attained in three to six hours, after a single dose. Continuous administration of therapeutic doses maintains the concentration at 4 to 6 mg. per 100 cc. (Sadusk *et al.*, 1940).

B. D. Davis, 1943, reports that dialysis experiments indicate that some of the sulfonamide drugs are *bound by the protein of the plasma.* This increases the solubility, but only the unbound drug is bacteriostatic. The fixation resembles absorption by activated charcoal. PABA is similarly absorbed (A. H. Andersen, 1945).

The concentration in *ascitic fluid* is generally 60 to 90 per cent of the blood level (A.M.A. Exhibit, 1944), and this holds presumably for extracellular tissue fluid.

The *cerebrospinal fluid*, after oral administration of sulfanilamide, contains almost as high a concentration as the blood (Marshall *et al.*, 1937). This holds also for sulfapyridine, but not for sulfathiazole, of which only traces are found (Sadusk *et al.*, 1940). Sulfaguanidine also gives only a fourth of the blood level. Four hours after a single *intrathecal injection* of 80 mg. of sulfanilamide, the cerebrospinal fluid contains 10 to 16 mg. per 100 cc., while the blood contains 1 mg. or less. It is eliminated from the cerebrospinal fluid in eighteen to twenty-four hours.

The *fluids of the eyes* show sulfanilamide within fifteen minutes after oral administration, in dogs. After a single massive dose of 0.2 Gm. per Kg., the maximal concentration is reached in about six hours, when the blood contained 19 mg. per cent, the aqueous humor 12 mg., lens 9.5 mg., vitreous 8.6 mg. After therapeutic doses of 0.075 Gm. per Kg. for six days, the fluids of the eye contained 2.2 to 3.9 mg. per cent, about the same as the blood. Local application of heat, atropine, physostigmine or dionine had no effect on the concentration in the aqueous humor; methylcholine caused a slight increase (Bellows and Chinn, 1939). *Sulfadiazine* also penetrates readily into agneous humor, *sulfathiazole* very little (Scheie and Souders, 1941, cats). In *human eyes* (blind) the concentration in the ocular humors was 1.5 to 3.2 mg. per cent after oral administration in clinical doses, and less than 0.1 mg. after local application to the conjunctival sac (Mengel, 1939).

Gastro-Intestinal Tract.—In dogs, appreciable concentrations of sulfanilamide are attained in the bile; pancreatic, gastric and intestinal juice, and saliva. The *bile* may attain bacteriostatic levels (Carryer and Ivy, 1939; H. Shay *et al.*, 1944). The concentration of sulfanilamide and sulfapyridine in *gastric juice* (dog, isolated pouch) is about three times that of the whole blood; it is less than the blood with sulfathiazole, sulfadiazine and acetylsulfanilamide (M. Cooke *et al.*, 1941). *Bronchial secretion*, with sulfadiazine, contains about 60 per cent of the blood level (C. M. Norris, 1943).

The *breast milk* of normally lactating women contains considerably higher concentrations than the blood, after administration of 2 to 5 Gm. of sulfanilamide. The ratio of conjugated, 35 to 84 per cent, is about the same as in the blood and urine. The total amount of sulfanilamide excreted by the milk did not exceed 0.23 Gm., or 1.6 per cent of the amount ingested, too small to be dangerous to the nursling (Hac *et al.*, 1939).

Prostatic fluid of dogs on 0.18 Gm. of sulfanilamide per Kg. daily contained concentrations that kill B. coli in twenty-four hours (Farrel *et al.*, 1938).

Human placenta transmits sulfanilamide freely, so that the maternal and fetal blood contain practically equal concentrations. It also passes promptly into the amniotic fluid (Speert, 1938).

The *liver* retains demonstrable traces of sulfapyridine up to forty days after the administration (W. H. Brown *et al.*, 1940).

The **urinary excretion** of sulfanilamide and sulfapyridine, free and acetylated, occurs by glomerular filtration with tubular reabsorption up to 80 per cent, similarly to urea (Marshall, 1940). In dogs, the average clearance of sulfanilamide is 36 per cent of the average urea, and 20 per cent of the average creatinine clearance (D. F. Green and Allison, 1938). With full sulfanilamide treatment the urinary excretion equals the intake almost quantitatively when equilibrium has been established, which requires two or three days (Marshall *et al.*, 1937). *Sulfapyridine* is excreted more slowly and may be demonstrated four to five days after withdrawal (Long and Feinstone, 1938). After a single dose of 2 Gm., 60 per cent is excreted in twenty-four hours, three-fourths conjugated; while in the blood only 10 to 20 per cent is conjugated (L. H. Schmidt and Hughes, 1939). *Sulfathiazole* is rapidly excreted by the urine, rendering it more difficult to maintain uniform blood concentration. The excretion is nearly 100 per cent, in twenty-four hours (Sadusk *et al.*, 1940). The percentage of acetylation for the different compounds was given above. The solubility of the acetylated sulfonamide is at least ten times greater than that of the other acetylated compounds. The sulfanilamide excretion is hastened by water diuresis and decreased in *renal insufficiency*. Smaller doses should be used in this condition (Marshall *et al.*, 1937; J. S. Stewart *et al.*, 1938).

Urinary concretions occur from the poorly soluble acetylated compounds, especially from sulfapyridine acetate, and the needle-shaped crystals may cause renal injury, especially if the water output is low. Uroliths have been found in rats, rabbits and monkeys after feeding them the drug for several days (Antopol and Robinson, 1939). Sulfanilamide may also precipitate, chiefly as acetate, if the urine is fairly concentrated. The concentration can be decreased by liberal water consumption, or more rapidly by intravenous injection of 5 to 10 per cent dextrose. Administration of *sodium bicarbonate* increases the renal clearance, by interfering with tubular reabsorption, and at the same time increases the solubility of the conjugated compound so that crystallization becomes minimal (O. L. Peterson *et al.*, 1943, K. H. Beyer *et al.*, 1944; the relations of *p*H to the solubility of sulfonamides are reported by H. A. Krebs and Speakman, 1946).

The mechanism of the antibacterial action is believed to be through interference with the metabolism of the bacteria, since the arrest of bacterial growth is so much more potent than the bactericidal action. The bacteriostasis diminishes the production of toxic substances and checks the spread of the invasion, so that the phagocytes and other antibacterial mechanisms of the body may bring about recovery from the infection. These defensive reactions of the host are generally necessary to complete the suppression of the bacteria (E. A. Bliss and Long, 1937; C. Lyons, 1928).

The bacteriostatic effect is presumably due to inhibition, perhaps analogous to narcosis, of one or more enzyme systems, most probably the respiratory oxidation-reduction system concerned in cell division, rather than of the more general anabolic-catabolic systems (R. J. Henry, 1944). This would be in harmony with their para-structure. The respiratory enzymes differ more or less for the varieties of bacteria, which would explain in part their different susceptibility to antibiotic substances (M. G. Sevag, 1944). An earlier explanation by Woods and Fildes, 1940, involved the concept of *competitive inhibition by biological analogues* (review, A. D. Welch, 1945), the competition of the sulfonamide with the chemically similar para-aminobenzoic acid which plays an essential part in the metabolism of certain bacteria. It is not required, however, by most pathogenic bacteria (review, J. S. Henry, 1944).

In vitro, the blood of patients containing therapeutically effective concentrations of sulfanilamide (10 mg. per 100 cc.) is bacteriostatic, but not generally bactericidal. This holds true also if such concentrations are added directly to cultures (Bliss and Long, 1937; Lockwood, 1938); but higher concentrations are bactericidal for susceptible bacteria, such as pneumococci (Rosenthal, 1937). Elevation of temperature within the febrile range has a marked effect; the antibacterial potency is sometimes 200 to 300 times greater at 39° than at 37° C. (H. J. White, 1939).

Phagocytosis is secondary to the humoral effect of the sulfonamides, for the bacteriostatic potency *in vitro* is about as great in serum as in whole blood (Lockwood, 1938); but sulfanilamide acts as opsonin in cultures (Finkelstein and Birkeland, 1938); and *in vivo* it is not effective if the polymorphonuclear leukocytes have been depressed by the injection of benzene (Bliss and Long, 1937; Macgraith and Collum, 1938). It has no chemotropic action on leukocytes (Coman, 1938). *Antibody* formation is not inhibited, but is additive to the sulfonamide bacteriostasis. This also summates with *bacteriophage*.

Respiratory Enzymes.—Sulfanilamide inhibits aerobic and anaerobic respiration in susceptible bacteria and other cells. The inhibition extends to the utilization of dextrose, dismutation of pyruvic acid, synthesis and utilization of tryptophane (M. G. Sevag, 1944). In fertilized *ova of sea urchin* (Arbacia), sulfanilamide (and azide) inhibits oxygen consumption and cell division, in concentrations that have no effect on unfertilized ova (K. C. Fisher *et al.*, 1944). On *plants*, sulfanilamide acts similarly to colchicine, arresting *mitosis* in midcareer, resulting in large cells with two or four times the normal number of chromosomes and so producing new plant varieties (J. M. Beal, 1941). Sulfanilamide inhibits the *germination of seeds*, as does also penicillin (F. Ribeiro, 1944, 1946). The enzyme system has not been definitely identified, but sulfonamide does inhibit certain dehydrogenases and carboxylase (review, R. J. Henry, 1944). However, inhibition of bacterial respiration *in vitro* is not a reliable criterion of chemotherapeutic bacteriostasis (O. Wyssa *et al.*, 1942).

Antagonistic Substances.—It was early recognized that the addition of peptone checks the antibacterial action of sulfanilamide on bacterial cultures; the maximal potency is therefore obtained only in the absence of protein cleavage products. Serum free from these does not interfere with the bacteriostasis (J. S. Lockwood, 1938; McIntosh and Whitby, 1938). A variety of other substances also antagonize sulfonamide bacteriostasis (C. M. MacLeod, 1940).

They belong to several categories (Henry, 1944): (1) Formation of inactive complexes: peptone and other proteins. (2) Independent stimulation of growth if conditions were suboptimal (dextrose, certain amino acids)

(3) Specific interference with sulfonamide action (para-aminobenzoic acid, procaine, probably methionine [J. S. Harris and Kohn, 1941] and mercuric chloride). A substance may belong to several of these categories, and others may exist.

Synergists.—*Carbamates* (especially butyl carbamate and ethyl carbamate; less effectively *urea*) antagonize the para-aminobenzoic and methionine inhibition of sulfonamide action (Tsuchiya *et al.*, 1942). They also increase the solubility of sulfonamides, and are of value in the treatment of gram-negative infections in man (L. Weinstein and McDonald, 1944). *Azochloramid* in low concentration also increases sulfonamide potency (Schmelkes and Wyss, 1942).

Inhibition of Nicotinic Acid.—Sulfapyridine interferes with the curative action of nicotinic acid in deficient dogs (R. West, 1941). Sulfapyridine and sulfathiazole inhibit the stimulating effect of nicotinic acid amide on the respiration of dysentery bacilli. Sulfanilamide does not have this action (Dorfman, Rice and Koser, 1941).

Para-Aminobenzoic Acid ("PABA") *Antagonism.*—In bacterial cultures, 1 mg. of this substance may inhibit the bacteriostatic effect of 5700 mg. of sulfonamide (D. D. Woods and Fildes, 1940; F. R. Selbie, 1940; Keltch *et al.*, 1941). "PABA" occurs as a metabolite in cultures of certain bacteria and appears necessary to their growth, as part of a metabolic enzyme system. Woods and Fildes suggested that the structural similarity of sulfonamides enabled them to substitute themselves for the "PABA," and so block the system. Addition of excess PABA would displace the sulfonamide and restore normal bacterial growth; the mutual displacement is somewhat analogous to that of oxygen and carbon monoxide hemoglobin. Similarly, bacteria that require pantothenic acid can be inhibited by its sulfonic acid analogue, and this can be neutralized by adding excess of pantothenic acid (Snell). However, Sevag, 1944, pointed out that only a few varieties of bacteria require para-aminobenzoic acid, and these are mostly saprophytes; diphtheria is the only pathogenic organism for which it is important. The explanation would therefore not apply to the therapeutic effects. R. J. Henry, 1944, concludes that the antagonism of peptone, necrotic tissue, and pus to sulfonamides is not due to their PABA content. He adduces examples where PABA inhibits sulfonamides in systems in which it could not be a metabolite. He suggests that the antagonism is "by some type of adsorptive phenomenon." Meta and para monoaminobenzoic acids are also effective antagonists of sulfonamides (Henry).

Procaine. para-aminobenzoyl-diethylaminoethanol and related local anesthetics derived from para-aminobenzoic acid, also inhibit the bacteriostatic action of sulfonamides. There is some evidence that antagonism is due to conversion into PABA (Henry). Much larger proportions are required (1 mg. of procaine to 20 mg. of sulfonamide; Ketch *et al.*, 1941); but the clinical use of these local anesthetics definitely lowers the effectiveness of action of sulfonamide bacteriostasis. Metycaine, which is not a PABA derivative, avoids this interference (C. C. Pfeiffer and Grant, 1944; O. L. Peterson and Finland, 1944).

Spontaneous Resistance to Sulfonamides.—The susceptibility to sulfonamide bacteriostasis varies greatly in different bacterial species and strains, in cultures and in disease, depending presumably on the enzyme systems, and on the presence of inhibitors such as PABA. Restriction of vitamin income during sulfonamide administration has been suggested (Sevag, 1944).

Acquired resistance (*fastness*) *to sulfonamide* develops gradually in some degree (never completely) on continued exposure in cultures, or by unsuccessful therapy. It usually extends to all the sulfonamides, but not to penicillin, and vice versa. It is transmitted to subcultures almost indefinitely and is probably due chiefly to selective survival of the more resistant strains. In some cases the surviving strains synthesize much more PABA, but others acquire fastness without this (Landy and Dicken, 1942). The fastness may sometimes be overcome by adding urea (Tsuchiya *et al.*, 1942).

Therapeutic Scope of Sulfonamides and Penicillin.—The introduction of sulfonamides initiated a change in the whole outlook of the treatment of bacterial infectious diseases, that of chemotherapy by interference with the nutrition of bacteria. As an illustration, the use of specific antitoxins in the United States decreased about 40 per cent between 1937 and 1939, although the two approaches do not exclude each other and may be used together if necessary. The discovery of penicillin has furnished another means of nonspecific chemotherapy, with a somewhat different but overlapping scope. These fields may be defined as follows (F. G. Blake, 1945):

(1) *Infections against which both sulfonamides and penicillin are more or less effective:* Certain gram-positive and negative cocci, hemolytic streptococci, pneumococci, staphylococci, streptococcus viridans, meningococcus and gonococcus. The potency varies for different sulfonamide derivatives and with the strain as well as the kind of bacteria.

(2) *Infections susceptible to sulfonamides but not to penicillin:* Gram-negative bacteria, colon, dysentery, Hemophilus influenzae, Friedländer's bacillus, Ducrey's bacillus. Good results are reported from sulfonamides in plague (Meyer, 1943). They appear fairly successful in trachoma, follicular conjunctivitis, lymphogranuloma venereum, molluscum granulosum, pemphigus vulgaris, dermatitis herpetiformis, lupus erythematosus disseminatus and actinomycosis. They are somewhat effective against experimental, but not against clinical, malaria.

(3) *Susceptible to penicillin but not to sulfonamides:* Syphilis, yaws, possibly other spirochetal infections, Clostridial gas gangrene.

Other infections and organisms resistant to sulfonamides include most animal and protozoan parasites, Rickettsias (typhus) and virus; anaerobic and hemolytic B. streptococci, Brucella melitensis, common cold, diphtheria, influenza, rabies, rheumatic arthritis and rheumatic fever, tuberculosis, tularemia, typhoid and paratyphoid.

Choice of Sulfonamide Compounds.—*Sulfadiazine* is at present the preferred compound for infections with streptococcus hemolyticus, pneumococcus, meningococcus, Friedländer's bacillus and influenza bacillus, also for local application to infected wounds (sterilized crystals) and for intravenous injection (sodium salt). *Sulfamerazine* has even rank for pneumococcal and meningococcal infections. *Sulfathiazole* ranks next for all these. It is preferred against staphylococcus, gonococcus and colon bacillus. *Succinylsulfathiazole* has a special field in bacillary dysentery; *sulfaguanidine* holds second place. *Sulfapyridine* has gone out of favor because of its nauseant action, and *sulfanilamide* similarly because of relatively frequent toxic reactions. It is still preferred for chancroid (N.N.R.).

With ordinary doses of sulfonamides, some forty-eight hours are required to attain the full therapeutic effect; relapse is likely to occur unless the administration is continued for a week or two after the clinical symptoms disappear and the blood cultures are negative. Success requires the cooperation of the natural defense mechanism, and the administration must be continued until this has been sufficiently developed. There is no evidence that sulfonamide therapy interferes in any way with this development (Curnen and MacLeod, 1942). Specific sera and other measures of accepted value should not be withheld from patients receiving sulfonamides; they appear rather to potentiate each other (Marshall, 1940; Lockwood *et al.*, 1938; Long and Bliss, 1937).

Animal experiments on mice led to the discovery of sulfonamide chemotherapy and are indispensable for its development. Their results differ only in degree from those of the clinic, but judgment is necessary in the transfer. The effective dosage differs widely, but this is due chiefly to differences in the absorption, conjugation and excretion: the effective blood concentration is similar in all animals. Acute experiments give little information about the toxicity of continued administration: Concentrations that are innocuous in a few hours may become toxic if they are maintained (Marshall, 1940). Data on the potentiation of chemotherapy and specific antisera are reported by Branham and Rosenthal, 1937.

Pneumococcus Infections.—Sulfonamide therapy is successful in lobar and lobular pneumonia, especially in children, for all types of pneumococci, although there are individual resistant cases that require penicillin. Ordinarily, the temperature drops critically within twenty-four to forty-eight hours after the sulfonamide is started, the other clinical symptoms improve promptly, and the blood becomes sterile. The mortality rate is greatly lowered. Sulfonamides may be used with the specific sera; indeed, with considerable potentiation. They do not interfere with typing. Sulfadiazine is preferred for oral administration. Sulfapyridine and sulfathiazole are equally effective, but are more likely to nauseate. Serious toxic reactions are unusual. Intravenous injection of the sodium salts of sulfadiazine or sulfathiazole is sometimes advisable and may be necessary in starting treatment, especially if absorption is prevented by vomiting, but they should not be used oftener than necessary, as the strongly alkaline solutions sclerose the veins. Oral administration must be continued until convalescence is established, to avoid relapses. The dosage is discussed under the individual drugs. Good results have been reported in pneumococcal meningitis (Neal *et al.*, 1940).

In mice pneumonia, sulfathiazole and sulfapyridine seem to be about equally effective. Pneumococci appear to become *"drug-fast"* by cultivation with increasing concentrations of sulfapyridine, so that they multiply with a hundred times the usual sterilizing concentration. Mice inoculated with such "fast" bacteria resist the doses of various sulfonamides which are ordinarily effective (L. H. Schmidt *et al.*, 1940; E. Netter, 1940). *Intermittent clinical administration* (for endocarditis) also renders the circulating pneumococci more resistant to sulfapyrazine in cultures (M. Hamburger *et al.*, 1942).

Meningococcus infections respond well to sulfonamides. Sulfadiazine is preferred, as in pneumococcal infections. A single dose of 2 Gm. is effective in eliminating carriers (P. H. Long, 1946).

Gonococcus Infections.—All sulfonamides are effective, but sulfadiazine or sulfathiazole is preferred. The dosage need not be so intensive as in pneumonia, although the action is chiefly through the blood. The effectiveness has greatly decreased, however, since the earlier reports, the failures rising from 15 to 35 and even 80 per cent, presumably by development of more resistant strains. It has been almost completely displaced by penicillin (Hench, 1946).

About 70 per cent of gonorrheal patients are cleared in five to seven days; another 10 to 15 per cent by a second course, and the remainder can be cured with penicillin. Hospitalized patients may receive an initial dose of 4 Gm., followed by 1 Gm. every four hours day and night for five days; ambulant patients, 1 Gm. four times daily for five days. Untoward results are not common with this dosage, and it is not necessary to check the concentration except in renal impairment. Fluid should be pushed. No local treatment should be applied (T. B. Turner and Sternberg, 1944). The benefits are independent of the disease and the extent of the involvement of the urinary tract. Practically all patients who are influenced at all by sulfanilamide are symptom-free by the end of the fifth day;. if improvement is not marked by then this drug should be discontinued. The patient should be seen by the physician at least every forty-eight hours, for *side reactions* are frequent and diverse, especially with ambulatory patients. Lassitude, dizziness, profound weakness and fatigue are indications for discontinuing the drugs, and then disappear in a day or two (Dees and Colston, 1937; B. Silver and Elliot, 1939; Pelouze, Barnes *et al.*, 1940).

The efficiency of sulfonamide in gonorrhea is increased by heat; in chick embryos also it is more effective above 37° C. than below (Bang, 1942).

Resistance of gonococci to sulfonamides appears inherent in the patient and not in the bacterial strain: In eighty-five mutually infected couples, both partners were resistant in only one instance, one partner in fifteen instances (A. H. Harkness, 1943).

Gonococcal ophthalmia neonatorum is also greatly benefited by oral sulfathiazole, 0.15 Gm. per Kg. of body weight, so that local therapy is not necessary (M. L. Blumberg and Gleich, 1943).

Urinary Infections Other than Gonococcal.—The efficiency of sulfonamides varies with the bacterial agent. They are less effective than mandelic acid against streptococcus faecalis, and less effective than methenamine against Escherichia coli. Sulfadiazine and sulfathiazole are preferred. This action is not affected by the reaction of the urine. Urinary volume should be at least 2000 cc. to prevent precipitation.

Streptococcus haemolyticus infections are more resistant to sulfonamide than are the meningo-, gono- and penumococci, but the therapy is quite effective against the bacteremia, lymphangitis, erysipelas and cellulitis; especially against early, diffuse lesions with maximal tissue invasion and minimal tissue destruction. It is ineffective against established abscesses, except to prevent their spread. It has no effect on toxemia. The presence of debris decreases the effectiveness. The invasive power is definitely decreased within eighteen hours (Lockwood, Coburn and Stockinger, 1937). The benefit in pharyngitis, tonsillitis and scarlet fever is limited chiefly to prevention of complications (N. Plummer *et al.*, 1945). In *erysipelas*, the inflammation is markedly improved within twelve hours, the lesions become dusky red or purplish within twelve to twenty-four hours and disappear completely in four to ten days, and the temperature falls within a few days by lysis (J. A. Toomey, 1938). Sulfathiazole is the preferred compound. Quinine potentiates sulfathiazole against hemolytic streptococcus infections of mice (B. K. Harned, Miller *et al.*, 1944).

Prophylaxis against Streptococcus Respiratory Infections.—The large scale controlled experience of the U. S. Army (Holbrook, 1944) and Navy (A. F. Coburn, 1944) indicates that the continuous daily administration of 0.5 Gm. of sulfadiazine strikingly decreases the incidence of these infections (by 50 to 75 per cent in the Army, by 90 per cent in the Navy reports). The rheumatic fever morbidity is also decreased. It is conceivable that resistant strains may be developed by unsuccessful cases (P. H. Long, 1946).

Untoward reactions are less than a half per cent with this dosage (as contrasted with 5 to 10 per cent for therapeutic doses). The more common are dermal, in the second or third week of administration. This may generally be resumed after a week's intermission. Serious cases were few, with a fatality rate of 1:46,000.

B. W. Billow and Albin, 1946, also report promising results in mass prophylaxis with 1 Gm. of sulfadiazine daily for five weeks. Only 0.3 per cent showed reactions, chiefly of the skin, none serious.

Rheumatic Fever.—Sulfonamides have little if any effect on the severity and duration of the acute attacks, and are considered useless or worse at this stage (H. F. Swift *et al.*, 1938). Penicillin also fails to influence the course. Prolonged daily administration of sulfonamides during the quiescent intervals appears to reduce the incidence of subsequent rheumatic attacks (review, Hench, 1946).

Wounds and Burns.—The systemic use of sulfonamides probably reduces the incidence of invasive complications of contaminated wounds, but it is difficult to maintain adequate concentrations in the blood under warfare conditions (P. H. Long, 1946). Local application of sulfonamides to wounds is of questionable value. Extensive experience in the war failed to show that it reduces the incidence or degree of infection (J. S. Lockwood, 1944). Dry sulfonamides produce irritation, sometimes even to abscess. Their use in *clean wounds* (including appendectomy stump) is inadvisable. They delay healing at least 50 per cent and promote excessive scarring. They may be justifiable in ulcerations and contaminated wounds (E. M. Bick, 1942; F. W. Taylor, 1942). The U. S. War

Department discontinued the local use, even on infected wounds (J.A.M.A., 1945, *128,* 597). Systemic toxic effects from local wound applications are rare (J. A. Key, 1943), but may be feared from extensive burned surfaces.

The wound is sprinkled with a light to heavy frosting of sterile sulfanilamide or sulfadiazine in 40 to 60 mesh powder, not more than 10 Gm. to a wound or 20 Gm. altogether. (Sulfathiazole is not suitable. It cakes and is more irritating.) A single packing with sulfanilamide may secure a local concentration of 800 mg. per 100 cc. for thirty-six hours. *Sulfapyridine* powder is an effective hemostatic for oozing wounds; sulfanilamide and sulfathiazole lack this effect (B. P. Cunningham, 1942).

Oral administration may start with an initial dose of 2 to 4 Gm. of sulfadiazine (or sulfathiazole), followed by 1 Gm. every six hours for eight days (P. H. Long, 1943).

Intraperitoneal application of sulfanilamide has been advocated for prevention and treatment of *peritonitis,* by spreading 4 to 10 Gm. of crystallized drugs in the area of greatest infection, and sprinkling 2 or 3 Gm. on the wound layers and dressings before closure. This gives a relatively high and persistent local concentration without irritation or toxic effects (H. C. Jackson and Coller, 1942).

Retardation of wound healing by local application of sulfonamides has been studied on denuded *cornea,* where it slows the restoration of epithelium and the growth of fibroblasts; the young cells appear to be more susceptible to the injury (J. G. Bellows, 1943). *Intraperitoneal application* to rats of powdered sulfanilamide produced practically no injury. Sulfathiazole caused only slight irritation; sulfapyridine proved excessively irritant, resulting in adhesions (T. D. Throckmorton, 1941). In *tissue cultures,* sulfathiazole is more toxic than the others, but under *clinical wound conditions* this is modified by solubility, so that the local toxicity decreases in the order of sulfanilamide > sulfathiazole > sulfapyridine > sulfadiazine. In all these, however, the concentration for toxic action is much higher than for bacteriostasis, and the recovery from any injury occurs readily when the drug is removed (F. Jacoby *et al.,* 1941); except with *intracranial application of sulfathiazole,* for this is likely to cause jacksonian epilepsy, in man and in animals. Sulfanilamide, sulfadiazine, sulfapryidine and sulfacetamide do not produce this effect (C. Pilcher *et al.,* 1942; A. C. Watt and Alexander, 1942). Electroencephalography on cats indicates that sulfanilamide is safer than sulfapyridine, sulfadiazine and sulfathiazole (C. Brenner and Cohen, 1943).

Preference for Local Application.—Sulfanilamide powder is generally preferred, not only because it is less likely to delay healing, but also because it is more soluble and less caking than the other sulfonamide powders (F. Hawkins and Hunt, 1942). *Sulfadiazine* ranks second. *Burns* may be sprayed with a 2½ per cent solution of *sulfathiazole in triethanolamine* solution, 8 per cent, which forms a thin eschar; other sulfonamides do not form an eschar. *Sulfathiazole* is indicated only in developed staphylococcus infections. It may be applied as a few drops of a 20 per cent suspension in water and covered with gauze (L. A. Chambers *et al.,* 1942). A 20 per cent sulfathiazole ointment has been recommended for burns (J. G. Allen *et al.,* 1942). *Succinylsulfathiazole* as 20 per cent ointment in hydrous wool fat liberates sulfathiazole gradually (Pulvertaft and MacKenzie, 1943). *Propylene glycol* was suggested as a menstruum for local application of sulfonamides to *mucous membranes,* 3 per cent sodium sulfathiazole or 10 per cent sulfanilamide, applied as such in the mouth and ear, but diluted with ten volumes of saline for the *nasal mucosa* (Yonkman, Craven *et al.,* 1942). However, the use of sulfonamide "nose drops" is questionable, as they sometimes lead to serious sensitization. Severe destruction has followed instillation of 5 per cent sodium sulfathiazole solution (Futch *et al.,* 1942).

Addition of sulfanilamide to *stored blood,* 20 mg. per 100 cc., was advised by N. Novak, 1939, to prevent bacterial contamination.

Skin Infections.—Cutaneous applications of sulfonamide should be limited to chancroidal and superficial primary pyogenic infections of the skin, such as impetigo. They should not be continued longer than five days; and, except for chancroid, they should not be used until other measures have failed, because the skin, conjunctiva and also the nasal mucosa present a special hazard of sensitization, so that future internal or external use may produce serious local or generalized, sometimes fatal, exfoliative dermatitis. "Over-the-counter" sales of sulfonamide ointments are too dangerous (H. N. Cole, 1943).

Chancroidal infections respond strikingly to locally applied sulfonamides. Sulfanilamide is preferred, as powder, diluted with 20 per cent of starch (Combes and Canizares).

Sensitization by Cutaneous Application.—Sulfonamides rarely produce direct local irritation, but continued local use on the skin, or eye or nasal mucosa, often sensitizes to both local and oral administration.This was noted in about 5.5 per cent of the patients (R. A. Darke, 1944). The dermatitis generally begins with an eruption at the site of application. There is also photosensitization to sunlight and ultraviolet rays (C. S. Livingood and Pillsbury, 1943; H. N. Cole, 1943; E. W. Abramowitz, 1944; Report of Council on Pharmacy and Chemistry, 1945, J.A.M.A., *128:*1024).

Experimental Sensitization.—Repeated injection of sulfonamides into guinea pigs does not produce an acute anaphylactic response; but if the sulfonamides are first conjugated with various proteins by the Landsteiner technic, they become antigenic, with cross sensitization to other sulfonamides (A. G. Wedum, 1942).

Intestinal infections indicate sulfonamides that are relatively insoluble, so that their action in the intestinal tract may be prolonged, with relatively low blood concentration. They affect the normal intestinal bacteria sufficiently to interfere with their manufacture of vitamins. *Sulfaguanidine* was introduced for this purpose by E. K. Marshall,

1941. Some toxic reactions have occurred in its clinical use (J. J. Bunting and Levan, 1944), and it has been largely displaced by the less toxic *succinylsulfathiazole* (*sulfasuxidine*) and *phthalylsulfathiazole* (*sulfathalidine*). This is chemically and therapeutically similar to succinylsulfathiazole, and is claimed to be less toxic and more bacteriostatic, effective also in colon infections, with a dosage of 3 Gm. daily. It is sparingly absorbed, and rapidly excreted in the urine, giving low concentration in the blood (M. H. Streicher, 1945). They are used especially for the treatment of bacillary dysentery, 1 to 3 Gm. every four to six hours, and the elimination of carriers (Painton and Hantman, 1945), to protect against infection in surgical operations on the stomach and intestines. Chronic colitis is not markedly benefited. Good results have been reported for epidemic neonatal diarrhea (Twyman and Horton, 1943) and Asiatic cholera (J. S. Huang, 1944). Altogether, however, the results have not equalled the early expectations; sulfadiazine and sulfathiazole appear to be quite as satisfactory in bacillary dysentery (2 Gm. followed by 1 Gm. every six hours).

Tuberculosis.—Several sulfonamide derivatives—notably *promin, diazone, promizole,* the more toxic *diamino diphenyl sulfone,* and some related compounds—restrain the development of experimental tuberculosis in guinea pigs (Hinshaw *et al.*, 1945). Clinical trials have given only equivocal or "mildly encouraging," or perhaps rather discouraging, results.

Experimental tuberculosis in guinea pigs differs materially from the clinical disease. Cooper and Cohn, 1945, believe that the action in guinea pigs involves anoxia which does not occur in man. The clinical dosage of promin is 1.3 to 3.2 Gm. per day, orally. It is very soluble and may be injected intravenously or parenterally.

Virus Diseases.—Only four of these—trachoma, lymphogranuloma venereum (A. A. Knight and David, 1939), inclusion blennorrhea and mouse pneumonitis—have been shown definitely to respond to sulfonamide therapy. It is doubtful whether these are true viruses; and the response might be due to interference with co-invaders (G. Rake *et al.*, 1942).

In *trachoma*, a single three week course of sulfanilamide in most cases results in rapid disappearance of the characteristic epithelial cell inclusions, the corneal lesion responding more promptly than the conjunctival, capillary hypertrophy than follicular. About half the cases are healed, another third improved, about an eighth show little or no change (W. G. Forster, 1940; P. Thygeson, 1940).

The virus of the common cold is not materially affected by sulfadiazine, and the course is not materially influenced. The development of secondary invaders is checked, but its routine use is not advised (R. L. Cecil *et al.*, 1944). *Canine distemper* was reported cured by sulfonamides (Marcus and Necheles, 1938; Dochez and Slanetz, 1938). *Rabies* was reported as prevented by sulfanilyl sulfanilate in about a third of the rabbits inoculated with fixed virus (F. D. Crea, 1939); but after the symptoms have started, treatment is unsuccessful (B. F. Hall and Evans, 1939). In *smallpox*, mitigation of the skin suppuration, fever and scarring was reported by McCammon as the result of sulfanilamide treatment.

Malaria is checked by sulfonamides, especially in monkeys (L. T. Coggeshall, 1938), and chicks (Coggeshall *et al.*, 1941), but it is not sufficient against human malaria (Coggeshall, 1943).

Other Animal Parasites.—Sulfonamides are not effective in rats and mice infected with trypanosomes, Endameba, Trichomonas, Giardia and Hexamita (Zurett and Culbertson, 1940) or Trichina (O. R. McCoy, 1938).

Actinomycosis.—Apparent clinical cure was reported by E. M. Miller and Fell, 1939.

Toxic phenomena in sulfonamide therapy vary greatly in kind and degree, depending on the compound used, on the susceptibility of the patient and on sensitization. Their occurrence has no relation to the therapeutic effects, nor is there a constant relation to the dosage or even to the blood concentration. The duration of the administration is important, and severe toxic phenomena may develop suddenly when a constant dosage has been maintained for several weeks without any symptoms. Most of the symptoms are mild, some are alarming, relatively few are severe enough to enjoin discontinuance of the medication; very few, indeed, have been fatal. As the serious intoxications are unpredictable, close daily supervision of the patients is imperative.

Minor toxic effects comprise nervous and gastro-intestinal symptoms, cyanosis, fever, rashes, acidosis, precordial and abdominal pain, urinary concretions and their consequences. *Dangerous toxic symptoms* are extensive rashes, jaundice, anemia, hemoglobinuria, uremia and granulocytopenia. These sometimes occur with low doses. *Fatal reactions* amount to less than 0.4 per cent, chiefly by uremia, sometimes by agranulocytosis, dermatitis and convulsions (Vilter and Blankenhorn, 1944; Sutliffe *et al.*, 1943).

Precautions against toxicity comprise frequent red and white blood cell counts and estimations of hemoglobin and icteric index. If the abnormalities are recognized early and the drug is withdrawn, they may increase for a few days, but then improve rapidly, especially if a transfusion is given. Patients who have had toxic reactions may develop more severe reactions on a second course (W. T. Tillett, 1940; C. F. Garvin, 1939; Lockwood *et al.*, 1938; Marshall, 1938; Long and Bliss, 1938). As far as is known, all other drugs may be prescribed during sulfonamide medication. Quinine and atabrine do not dispose to untoward reactions, except perhaps to emesis (Harned and Etteldorf, 1944).

Patients who had toxic reactions in the first course are likely to develop toxic effects in a subsequent course, even if considerable time has elapsed. A different sulfonamide should be administered, as the reactions are less frequent (17 per cent) than when the same drug is administered (69 per cent; H. F. Dowling *et al.*, 1946).

Relative Toxicity.—*Sulfonamide* gives the greatest frequency of toxic reactions: about half of the adult patients, a fifth of the children. Cyanosis, acidosis, anemia and fever are especially frequent, nausea is relatively infrequent and urinary injury is insignificant. *Sulfadiazine* gives the fewest reactions (Vilter and Blankenhorn, 1944). With a single dose of 2 Gm., used in respiratory prophylaxis, only 0.5 per cent had any toxic manifestations, and these were serious in only 0.035 per cent. as high fever and mental disturbance (R. V. Lee, 1944). *Sulfathiazole* produced reactions in about a fourth of the patients receiving a single course; about half of these were allergic (Kent and Diefendorf, 1945). It causes vomiting in about 10 per cent of the patients, but not sufficient to prevent its administration. Fever, rashes and conjunctival congestion are more frequent than with sulfapyridine. Renal and hematopoietic effects are relatively slight and transient. The incidence of other toxic reactions is low. Its ready absorption and excretion facilitate even concentrations (Reinhold *et al.*, 1940). *Sulfamethylthiazole* is more toxic than sulfapyridine (Van Dyke *et al.*, 1939). Polyneuritis has been reported from its use; and especially from *sulfanilyl sulfanilamide* (Wighton and Johnson, 1938); it may also occur from sulfanilamide, clinically and in animals (Ornsteen and Furst, 1938), but is rare. *Sulfapyridine* is definitely more toxic than sulfanilamide on the basis of their concentration in the blood; but on oral administration sulfapyridine appears less toxic (Wien, 1938), because it is completely absorbed. However, it often produces severe nausea and vomiting; cyanosis and acidosis are less; severe leukopenia is apparently more common, especially with children; renal concretions and injury are more marked and call for greater water intake. The other toxic phenomena are closely similar to those from sulfanilamide (W. H Brown *et al.*, 1940). *Acetyl sulfapyridine* is more toxic to animals than is the free form and may cause marked lowering of the kidney function (creatinine clearance) clinically (Marshall and Litchfield, 1939; W. H. Brown *et al.*, 1940).

Sensitization by Oral Administration.—About a third of the patients treated with sulfonamide drugs develop a hypersensitivity sufficient to interfere with their subsequent use (R. H. Lyons and Balberor, 1941). This allergy is manifested chiefly by fever, skin eruptions and conjunctivitis. It sets in usually about nine days after starting the administration, and may persist for at least two years (J. R. Gallagher, 1939). It may show up in a later course even when the initial course was without symptoms (J. Nelson, 1942). Any one sulfanilamide sensitizes to all the others.

The allergic hypersusceptibility (but not the other toxicities, such as liver injury or hemolytic anemia) may be recognized by a wheal *reaction to intracutaneous injection* of 0.5 cc. of blood serum of patients receiving sulfonamide therapy, even though these are without symptoms. It is probably provoked by a combination of the sulfonamide group with plasma protein (W. B. Leftwich, 1944).

Untoward reactions may be grouped as (1) *allergic sensitization*, especially fever, skin eruptions and conjunctivitis; (2) *direct toxic;* (3) *mechanical*, from the precipitation of the drugs or their acetyl conjugates in the urinary passages (G. T. Kent and Diefendorf, 1945).

Fever, often with dermatitis, and with or without conjunctivitis, occurs in about a fourth of the patients, less often with sulfadiazine and sulfapyridine than with sulfanilamide and sulfathiazole. It is a sensitization phenomenon, developing usually between the seventh and tenth day of administration, sometimes on the second or third, with a peak on the ninth day. It is twice as frequent in patients who had a previous course of the same sulfonamide, although most of these did not have fever in the first course; but the fever is less frequent if a different sulfonamide was used in the first course (Dowling and Lepper, 1944). It may set in after a dosage has been decreased, so that it does not depend on concentration of the drug. It may occur without other toxic symptoms. Most commonly the temperature rises slowly and returns to normal in two days after the drug is stopped. Treatment may then be cautiously resumed, preferably with another sulfonamide. A few patients develop high fever twenty-four hours after starting the treatment. Fever also usually precedes the more serious effects of acidosis, acute hemolytic anemia, agranulocytic angina, dermatitis, toxic neuritis and hepatic jaundice (Lockwood *et al.*, 1938; Hageman and Blake, 1937).

Skin eruptions and conjunctivitis are common with systemic as well as local administration of all sulfonamides. They often accompany the fever and are also due to allergic sensitization. Sulfathiazole is perhaps especially subject to this (B. Shaffer *et al.*, 1943). The rashes are of various types and degrees, often resembling confluent measles, but sometimes take other forms, such as purpura. They may be evoked by sunlight or ultraviolet radiation (H. B. Blum, 1940; R. G. Park and Platts, 1942). They generally disappear in two or three days after withdrawal, and the administration may then be cautiously resumed, preferably with another sulfonamide (W. H. Brown *et al.*, 1940). If they extend over the whole body, however, and if the itching is severe, it should be a warning to discontinue altogether, as they may turn into acutely fatal exfoliative dermatitis. Such has been reported for ordinary doses of sulfathiazole (Weinstein and Domm, 1941) and sulfadiazine (R. D. Johnson, 1944). Severe pemphigus has occurred with sulfamerazine (L. A. Kasselberg, 1943). Bronchial asthma as a manifestation of sulfonamide therapy has been observed (Randolph and Rawling, 1944), but is rare.

Nausea and vomiting are especially common with sulfapyridine, and may be so severe as to preclude its oral administration. They appear to involve both local and systemic actions. A 1 Gm. dose of sulfapyridine delays the emptying time of the human stomach by an average of nearly a third (Northrup and Van Liere, 1940). A few patients have severe diarrhea and abdominal pain. Gastric disturbance is much less frequent with sulfathiazole, still less with sulfadiazine and exceptional with sulfanilamide.

Nervous disturbances as direct actions of the sulfonamides are frequent but usually mild: confusion, restlessness, dizziness, headache, nausea, vomiting; irritable, depressed or elated moods, lassitude and fatigue. They disappear completely after discontinuing the drug. Controlled tests on normal men showed no significant effect on reaction time, coordination and mental efficiency during the ordinary course of sulfadiazine or sulfathiazole (Reynolds and Shaffer, 1943; A. H. Price and Pedulla, 1944). Not infrequently, however, *serious nervous changes* develop in patients under sulfonamide treatment, especially if there was preexistent disease of the nervous system. They include severe melancholia (Lockwood *et al.*, 1938), aphasia, agraphia, stammering, toxic psychosis, peripheral neuritis, encephalomyelitis, optic neuritis, transitory myopia, blindness, convulsions (S. C. Little, 1942).

Animal experiments indicate that all sulfonamide drugs have toxic effects on the nervous system. Large doses abolish weak conditioned reflexes in dogs (Gantt and Marshall, 1945). Chickens develop peripheral neuritis, involving also the spinal cord and to a less extent the brain, the toxicity increasing from sulfanilamide (least) to sulfapyridine, sulfathiazole, and sulfamethylthiazole (most) (R. N. Bieter *et al.*, 1941). In *dogs*, different phenomena were evoked by sulfapyridine and sulfanilamide with doses above therapeutic levels (C. F. Morgan *et al.*, 1944). Sulfanilamide administration to *rats* does not alter their susceptibility to volatile and gaseous *anesthetics*, but materially increases their susceptibility to poisoning by the briefly acting barbiturates, especially the thiobarbiturates (Adriani, 1939); narcosis and fatality by papaverine is also increased (Glaubach, 1939). Sulfapyridine is reported to increase the intensity, duration and toxicity of the effects of morphine and codeine (Glaubach, 1941).

Cyanosis occurs in most patients with sulfanilamide, infrequently with sulfapyridine, rarely with sulfathiazole and sulfadiazine (R. R. Kracke, 1944). It develops generally about the third day of sulfanilamide administration, but sometimes within twelve hours, as a slate gray to deep blue color, first seen in the lips and finger nails, and spreading over the entire body. Its intensity does not parallel the drug concentration of the blood (Wendel, 1939). It clears rapidly on withdrawal. It is not a serious complication and does not call for decrease of dosage.

The mechanism of the cyanosis was at first in dispute, but it is now agreed that it is due to methemoglobin, although there may still be a few discordant voices (Chesley, 1938; F. H. King and Leslie, 1938). This pigment would be expected from the analogy of the clinical structure of sulfanilamide to aniline, while the sulfamido group could give rise to sulfhemoglobin. The latter, however, is present only in traces, regardless of the administration of sulfates (which were said to form this pigment; J. P. J. Paton and Eaton, 1937; Discomb, 1937). A. P. Richardson, 1940, reports that the sulfhemoglobin formation in mice depends on the sulfur content of the diet, and that it is increased by giving thiosulfate, sulfur, or potassium sulfonate, not by magnesium sulfate or thiourea.

The degree of cyanosis is parallel to the oxygen-carrying power (Hartmann *et al.*, 1938), and depends on the methemoglobin content, being detectable with 5 per cent and striking with 15 per cent of the hemoglobin in this form; 25 per cent has been reported. These levels are not high enough to cause symptoms of oxygen deficiency, except perhaps in pneumonia and in cardiac insufficiency. The cyanosis can be prevented or promptly removed by the administration of methylene blue, 0.065 to 0.130 Gm. every hour by mouth, or 1 to 2 mg. per Kg. intravenously (Wendel, 1939; Hartmann *et al.*, 1938; Campbell and Morgan, sulfapyridine, 1939; Vigness *et al.*, 1940; Richardson, 1939).

Marshall and Walzl suggested that the cyanosis is due to aniline black; Fox, Cline and Ottenberg, 1939, produced a purple dye by irradiation of sulfanilamide, but the spectrum is quite different from that of the sulfanilamide cyanosis, which is that of methemoglobin (Wendel, and Wendel, 1939). Oxidation of sulfanilamide and sulfapyridine by hydrogen peroxide also results in colored oxidation products which are absorbable by the fat of the envelope of the red corpuscles, without affecting the oxygen capacity. Oxidation products of sulfanilamide have been isolated from the urine (G. V. James, 1940) and may be responsible for cyanosis in the absence of met- and sulfhemoglobin.

Clinical acidosis occurs in about 3 per cent of the patients receiving sulfanilamide (Long and Bliss, 1938) and probably less frequently with sulfapyridine. It is not of important degree, but has prompted the routine administration of 0.5 Gm. of sodium bicarbonate for each gram of sulfanilamide. A. F. Hartmann, 1939, considers the decrease of plasma bicarbonate secondary to hyperpnea, and therefore primarily as a CO_2 deficit alkalosis, so that routine administration of alkali would not be indicated. The changes in dogs with large doses of sulfanilamide are also of the type of compensated CO_2 deficiency (McChesney *et al.*, 1939). Dogs receiving sulfanilamide for twelve days in doses equivalent to the clinical, showed slight decrease (5 per cent) of serum CO_2, without significant changes of *p*H. Administration of citrate prevents the CO_2 decrease (A. H. Free *et al.*, 1943). Sulfanilamide lowers the CO_2 combining power of the blood in man

(H. Southworth, 1937), perhaps by specific inhibition of carbonic anhydrase, which has been demonstrated for sulfanilamide, but does not occur with sulfapyridine (T. Mann and Keilin, 1940).

Ability to tolerate high altitudes (20,000 feet) is not significantly altered in normal persons by full therapeutic doses of sulfathiazole (E. W. Peterson *et al.*, 1945), although it was reported as improved in rabbits and dogs (F. L. Lawson, 1942).

Acute hemolytic anemia, destroying a third to over half of the red blood corpuscles within one or two days, may occur with any of the sulfonamides, in about 4.3 per cent of the clinical courses (C. B. Hendricks, 1942), irrespective of dosage or concentration in the blood. It begins usually on the first to third day of administration and reaches its acme between the third and seventh day, usually about the fifth day, but it may be delayed till the tenth day or longer, and it may increase for a day or two after the drug is withdrawn. No definite predisposing factors have been discovered, except that it tends to recur if a second course is given (W. B. Wood, 1938). It is perhaps more common with sulfanilamide, but occurs with sulfapyridine (Ravid and Chesner, 1940), sulfathiazole (Quick and Lord, 1941) and sulfadiazine (N. H. Boyer, 1943). The cause of the hemolysis is not known. There is marked hematogenous jaundice and hemoglobinuria, often with some hematoporphyrin. It is usually accompanied by high leukocytosis, fever, weakness and other symptoms which may be secondary to the hemolysis. Liver and renal injury are present in some cases. The erythrocytes do not show increased fragility (Spring and Bernstein, 1940). Erf and MacLeod, 1940, found increased urobilinogen excretion in about a third of pneumonia patients treated with sulfapyridine. Jaundice is usually due to hemolysis, and is a definite warning to discontinue the medication.

Secondary anemia is common with all sulfonamides, regardless of dosage, averaging nearly 40 per cent (Hendricks, 1942). The red corpuscles decrease gradually, sometimes to half of the normal, and return to normal when the drug is stopped. *Aplastic anemia* has been reported with sulfathiazole (L. M. Meyer and Perlmutter, 1942).

Sulfonamide Anemia in Animals.—In *white rats*, daily administration of large doses (1 Gm.) of sulfanilamide develops marked decrease of the red blood cells and other changes of macrocytic anemia. The bone marrow shows initail myeloid stimulation, then depression (Higgins and Machella, 1939). The anemia is accompanied by congestion of the spleen with extensive deposits of brown, granular pigment, the histologic picture returning to normal in four weeks after discontinuing the drug (Rimington, 1938). In *mice*, small Heinz bodies appear in most mature erythrocytes within a day after beginning the administration of sulfanilamide. They consist of cholesterol and protein with very little iron (A. P. Richardson, 1942). Sulfadiazine and sulfamerazine produce hemolytic anemia in 50 per cent of mice when their blood concentration reaches about 33 mg. per 100 cc.; sulfapyridine does so with 2.8 mg. per cent (Latven and Welch, 1944). Sulfanilamide is about twice as potent as sulfapyridine (A. P. Richardson, 1939).

Decrease of blood platelets, leading to severe thrombopenia purpura, is occasionally produced by sulfonamides (Kracke and Townsend, 1943).

Decrease of the prothrombin level may occur by inhibition of the intestinal bacteria which produce vitamin K (Daft *et al.*, 1942).

The leukocyte count tends to fall during the first week of the clinical administration and generally remains low for the next two weeks (C. J. C. Britton and Howkins, 1938). The acute leukopenia is more frequent with sulfapyridine, and may occur with small doses and brief administration (W. H. Brown *et al.*, 1940). It does not ordinarily involve the granulocytes (Bigler *et al.*, 1938).

Agranulocytosis occurs in about 0.9 per cent of sulfonamide therapy (C. B. Hendricks, 1942); fatal cases have been reported for sulfapyridine (W. H. Brown *et al.*, 1940) and sulfathiazole (P. C. Kennedy and Finland, 1941). It has been produced in weanling rats and corrected by administering liver (S. S. Spicer *et al.*, 1942; A. Kornberg *et al.*, 1943). On the other hand, sulfadiazine is useful to prevent bacteremia in agranulocytosis from other agents (H. Tarnower, 1945). *Interstitial myocarditis* with eosinophilic cellular infiltration is reported by A. J. French and Weller, 1942, as a common occurrence in autopsies of patients who had been recently treated with sulfonamides.

Hepatitis, with diffuse necrosis, occurs exceptionally (P. A. Herbet and Scaricacottoli, 1945), especially with exfoliative dermatitis (C. F. Garvin, 1938). Histologic liver injury has been described in children by Menten and Andersch, 1943. Jaundice, however, is generally due to hemolytic anemia. Indeed, sulfonamides do not aggravate the dysfunction of chronic liver damage, and they improve acute hepatitis associated with bacterial infection. With severe portal cirrhosis, serious toxic effects, other than on the liver, are exceptionally frequent (O. L. Peterson *et al.*, 1943).

Renal damage by sulfonamides may be of two types: (1) obstruction of the urinary tubules by crystals of the sparingly soluble acetylated derivatives (sulfanilamide is not subject to this); and (2) direct toxic renal lesions, tubular or sometimes interstitial, not dependent on obstruction. This is the most frequently fatal sulfonamide complication (Vilter and Blankenhorn, 1944). The renal injury is largely independent of the dose; fatalities have occurred in a range of 0.6 to 41 Gm. (F. D. Murphy *et al.*, 1944).

Urolithiasis, with renal and ureteral obstruction, is a fairly common complication of all sulfonamide therapy, except sulfanilamide, unless precautions are taken, especially in hot climates. It may become serious if not treated promptly. It is due to the crystallization of the acetylated compounds. This is influenced chiefly by the concentration of the drug, urinary stasis, *p*H and temperature of the urine (R. W. Barnes and Kawaicki, 1943). It is prevented by liberal water income, maintaining the daily urine volume above 2000 cc., and keeping it alkaline. Penna and Christopher, 1946, recommend daily intravenous injection of 15 Gm. of sodium bicarbonate for intensive sulfadiazine therapy.

The renal obstruction symptoms may develop on the second day or later, with abdominal or renal pain, hematuria, oliguria and nitrogen retention. Sulfapyridine urolithiasis occurs fairly constantly in rabbits, rats and monkeys, but not in dogs and mice, probably because these do not acetylate readily (Molitor and Robinson, 1939; Antopol and Robinson, 1940). Sulfadiazine lesions have been studied in dogs. The crystals formed high in the descending loop of Henle, with inflammatory reaction extending to and involving the glomeruli (B. Maisel *et al.*, 1942).

Direct toxicity to the kidneys is perhaps still somewhat in dispute. Prolonged administration of sulfanilamide to rats with nephrotoxic nephritis did not aggravate the course (Smadel and Swift, 1939). Nephrotoxic action has been observed clinically, however, in the absence of tubular obstruction (Priest, 1945). Sulfadiazine is reported to be more toxic than sulfamerazine and sulfamethazine (L. H. Schmidt *et al.*, 1944).

The **general toxicity** of sulfanilamide, as determined on animals, is low both for acute experiments and for continued administration, but the two are not necessarily parallel for different compounds. The acetyl derivatives are somewhat more toxic. The *acute fatality* of rats with oral administration of a single dose of *sulfanilamide* suspended in acacia is none at 3 Gm. per Kg., 20 per cent at 4 Gm., and 50 per cent at 10 Gm. (Murayama and Leake, 1938). With intraperitoneal injection into rabbits, 0.4 Gm. per Kg. had no effect, 1.0 Gm. caused mild symptoms, 1.5 marked symptoms (weakness of the legs, dyspnea and spasticity), and 2 Gm. were fatal to some of the rabbits and also to some of the cats. These showed chromatolysis of the central nervous system, especially in the spinal cord. Those which survived and were killed a week later showed no changes in the liver or kidneys (Hawking, 1937). Kohn-Richards, 1940, reports that the toxic effects resemble those of picrotoxin and that urethane, barbiturates and bromide are somewhat antagonistic, especially to the convulsions. Intravenous injection of 0.17 Gm. of sulfanilamide per Kg. in dogs and cats does not alter the blood pressure. *Sulfapyridine* injected by vein into dogs had little if any toxic effects with 0.1 Gm. per Kg.; 0.2 Gm. caused slight ataxia and muscular twitching; 0.3 Gm. caused vomiting, tremors and convulsions; 0.5 Gm. was fatal in two of five dogs (Marshall and Long, 1939). *Sulfathiazole* was studied on animals by H. A. Walker and van Dyke, 1941; *sulfadiazine* by W. H. Feinstone *et al.*, 1940; *sulfamerazine* by A. D. Welch *et al.*, 1943.

Continued oral administration of sulfanilamide to dogs, rabbits or rats at the rate of 0.2 Gm. per Kg. three times daily was not fatal after eight or more doses, but several of the animals had convulsions; none had anuria or renal or liver changes (Geiling, Coon and Schoeffel, 1937). Adult rats receiving 2 Gm. per Kg. of body weight daily, in acacia suspension, for five days, then 1 Gm. for five weeks, gradually lost weight and developed greatly enlarged spleens (Murayama and Leake, 1938). Parenteral injection for fourteen days into white mice produced marked hemosiderosis in the spleen, suggesting increased blood destruction. No pathologic lesions were found in the liver and kidneys (Hageman, 1937).

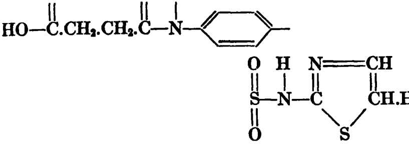
The *influence of diet* on sulfanilamide toxicity is reported by Kapnick *et al.*, 1942. *Thiamine deficiency* increases the toxicity of sulfapyridine (V. V. Cole and Harned, 1942). The addition of sulfapyridine (H. D. West *et al.*, 1943) or succinylsulfathiazole (E. Nielsen and Black, 1944) to the food of rats produces alopecia and other symptoms of *pantothenic acid* deficiency, alleviated by adding this substance or inositol, increased by biotin and folic acid. Sulfonamides also produce *vitamin K deficiency* in rats, parallel to their bacteriostatic effects on coliform bacteria. Ordinary absorbable sulfonamides are more effective than sulfaguanidine and succinylsulfathiazole (A. Kornberg *et al.*, 1944). The latter produced accumulation of calcium in the liver, and hepatic enlargement (Pilgrim and Elvehjem, 1945).

Various sulfonamides have different effects on the *blood sugar level and on liver glycogen* formation and storage (Greisheimer *et al.*, 1941). The *basal metabolic rate* of rats drops sharply when sulfonamides are fed. This is accompanied by thyroid hyperemia and hyperplasia, the phenomena of thyroid deficiency, including changes in the cells of the anterior pituitary (J. B. Mackenzie and Mackenzie, 1944). The effects resemble those of thiourea. The hyperplasia is not influenced by administering iodides, but it is inhibited by giving thyroid or by hypophysectomy. The hyperplasia is attributed to failure of thyroxin synthesis (Astwood *et al.*, 1943). Sulfonamides impede the *in vitro* conversion of iodide by slices of thyroid into diiodotyrosine and thyroxin (A. L. Franklin and Chaikoff, 1944). If sulfonamides are administered to rats during the latter part of gestation, the fetus shows almost complete absence of calcification. This is attributed to inhibition of phosphatase (R. Benesch *et al.*, 1945).

The *autonomic system* is but little affected by sulfonamides. Sulfanilamide, 1:1000, has no effect on *excised intestine* of rabbit and *uterus* of guinea pig (Hawking, 1937). Sulfonamides do not affect the response of the isolated intestines of rabbits and guinea pigs to epinephrine, acetylcholine, neostigmine, histamine and barium chloride, but they do inhibit the effects of *nicotine*. This is not antagonized by para-aminobenzoic acid. The response of striated muscle and the general toxicity of nicotine for frogs is not inhibited by sulfonamides (E. P Pick *et al.*, 1944). The excised *frog heart* is stimulated, then depressed; the maximal stimulation occurs with 0.25 per cent; 0.5 per cent slows to half or stops (Mendenhall and Shreeve, 1939). Sulfanilamide is directly toxic to the *skeletal muscle* of frogs (Litchfield, 1939). Administration of sulfanilamide or sulfapyridine inhibits the *calcification of egg shell*, so that this is soft, thin and pitted. This action is much weaker with other sulfonamides. It occurs without other symptoms and has been attributed to inhibition of carbonic anhydrase (Keilin and Mann), which is presumably necessary to shell formation (Benesch *et al.*, 1945). The evidence is not conclusive (R. Bernard and Genest, 1945). The *luminescence reaction* of luciferase on purified luciferin of cypridina is retarded (but not diminished) by sulfonamides, also by para-aminobenzoic acid and by urethane (F. H. Johnson and Chase, 1942). Sulfanilamide is reported to stimulate the formation of roots on *plant cuttings*.

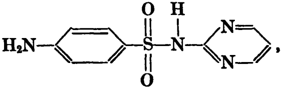
PREPARATIONS.—Sulfonamides generally are but sparingly soluble in water, but dissolve freely in dilute mineral acids and in alkali hydroxides. The sodium compounds are soluble and are used parenterally in sterile water for injection. The following sulfonamides are arranged in alphabetic order:

Succinylsulfathiazole, U.S.P., "*sulfasuxidine*,"



resembles sulfathiazole, but is little absorbed (not more than 4 per cent) after oral administration, so that the toxicity is low (A. D. Welch *et al.*, 1942). It is used for its bacteriostatic effect on the gastro-intestinal tract, and is safer than sulfaguanidine. It is employed for prophylaxis in intestinal operations, and for the treatment of acute bacillary dysentery, and on carriers of these bacteria. It is not effective against typhoid. The *preoperative dosage* is 0.25 Gm. per Kg., followed by the maintenance dose of 0.04 Gm. per Kg. every four hours, day and night, continued for one or two weeks after the operation. This maintenance dosage for seven days is also effective in eliminating carriers of Sonne dysentery (J. F. Painter and Hantman, 1945). Succinylsulfathiazole occurs as a white, crystalline, almost tasteless powder, slightly soluble in water (1:4800), soluble in dilute alkali. *Succinylsulfathiazole Tablets*, U.S.P., are usually available as 0.3 and 0.5 Gm.

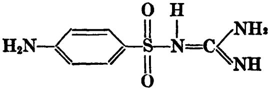
***Sulfadiazine**, U.S.P.,



is at present the preferred preparation for all internal administration. It has the advantage of more uniform absorption, sustained blood concentration and relatively low acetylation. It is as effective as any of the others, less nauseant than sulfapyridine and sulfathiazole; other toxic reactions are probably also less frequent. Sulfadiazine is administered in powder or tablets. The dosage is aimed to maintain the blood level about 10 to 15 mg. per cent in severe infections, 5 to 10 mg. in mild. In *severe infections*, the administration should start with 0.1 Gm. per Kg. of body weight, followed by 1 Gm. every four hours with 2 Gm. of sodium bicarbonate, day and night, until the temperature has been normal for seventy-two hours, when it may be discontinued. The daily urine output should be kept above 1000 cc. Oliguria or hematuria indicates that the drug should be discontinued and fluids forced. The alkali increases the solubility of the acetylation products in the urine (D. R. Gilligan *et al.*, 1943). Its absorption is slower and less complete than with sulfathiazole or sulfanilamide, but its excretion is also slower, so that relatively high concentrations are attained in the blood with smaller doses. Acetylation is also less. *Toxic reactions* are relatively infrequent, occurring in about 8 per cent of patients; the most frequent are renal. Nausea, vomiting, drug fever and cyanosis are rare, hemolytic anemia and agranulocytemia are still rarer. Acidosis is absent. In *mild infections*, the initial dosage may be half of the above. Sulfadiazine is a white powder, stable in air, darkening slowly in light. It is slightly soluble in water (8 mg. to 100 cc. at room temperature, 12.3 mg. per cent at 37° C.) Human serum dissolves 160 mg. per cent at 37° C. Average dose, 2 Gm., 30 grains. *Sulfadiazine tablets*, U.S.P., are usually available as 0.3 and 0.5 Gm.

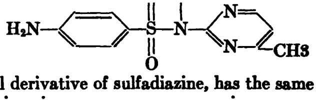
Sulfadiazine Sodium, U.S.P., is freely soluble in water (1:2). The 5 per cent solution of *Sterile Sulfadiazine Sodium*, U.S.P., is suitable for intravenous injection when prompt action is imperative or when vomiting prevents oral administration. The dosage is the same as by mouth. The solution is strongly alkaline (*p*H 9 to 10), and tends to produce thrombosis, so that it should be used only once or twice; never intramuscularly, as sloughing or gangrene results. The total dosage should usually not exceed 5 Gm.

Sulfaguanidine, U.S.P.,



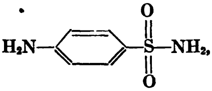
sulfanilylguanidine monohydrate, is fairly soluble in the intestinal contents, but is not readily absorbed, so that its blood level rarely exceeds 5 mg. per 100 cc., if it is properly administered. It is intended for local action in the intestinal tract, to secure bacteriostasis. It is used as *prophylaxis in colonic surgery*, 0.05 Gm. per Kg. of body weight, every eight hours, day and night, for five days before and seven days after the operation. Its usefulness in the treatment of *bacillary dysentery* is limited. The dosage is 0.05 Gm. per Kg. every four hours day and night till the stools are definitely decreased, then every eight hours for at least three days. If improvement does not occur in seven days, further administration is not likely to be successful. It is also used in treating carriers of bacillary dysentery (J. J. Bunting and Levan, 1944). Toxic reactions are relatively infrequent, but nearly a tenth of patients develop fever (Bunting and Levan); severe intoxication with rash and hematuria has been reported (S. L. Cole, 1942). Sulfaguanidine occurs as a white crystalline powder, sparingly soluble in water, freely soluble in dilute acids, insoluble in dilute alkali. Average dose, 2 Gm., 30 grains. *Sulfaguanidine Tablets*, U.S.P., are usually available as 0.3 and 0.5 Gm.

Sulfamerazine, sulfamethyldiazine,



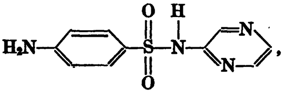
a methyl derivative of sulfadiazine, has the same field as sulfadiazine in pneumococcus, meningococcus, gonococcus and streptococcus infections (Macartney *et al.*, 1942). It is absorbed more rapidly and excreted more slowly than sulfadiazine, so that effective blood concentration is attained and sustained with about half the dosage, and the interval between doses may be doubled (Hageman *et al.*, 1943). It is well tolerated; nausea and other untoward effects are about as with sulfadiazine (H. F. Dowling *et al.*, 1944). Peripheral neuritis has been reported, but is exceptional. Urinary precipitation should be less (R. A. Goodwin *et al.*, 1942). A larger proportion is acetylated, but the acetylated as well as the unconjugated substance is more soluble than with sulfadiazine. Dowling *et al.*, however, found renal calculi rather more frequent, although not serious. Sulfamerazine was first described by R. A. Robbins *et al.*, 1940; its pharmacology and toxicology were studied by A. D. Welch *et al.*, 1943. The *clinical dosage* to keep the blood level at 10 to 15 mg. per 100 cc. starts with an initial dose of 3 or 4 Gm., followed by 1 Gm. every eight hours, continued for seventy-two hours after the temperature has returned to normal, unless there are toxic complications. Sulfamerazine occurs as a white, tasteless crystalline powder, which may darken on exposure to air. It is soluble in dilute acids and alkalis; slightly soluble in water, 22 mg. in 100 cc. at 25° C. Average dose, 2 Gm. *Sulfamerazine Tablets*, U.S.P., usually contain 0.5 Gm. *Sulfamerazine Sodium*, U.S.P., and *Sterile Sulfamerazine Sodium*, U.S.P., are freely soluble in water (1:3). The dosage for severely ill patients is 0.05 Gm. per Kg. of body weight, as 5 per cent solution, followed to 0.025 Gm. per Kg. at twelve hour intervals. The blood concentration should not exceed 15 mg. per 100 cc.

Sulfanilamide, U.S.P., p-amino benzene sulfonamide, "Prontylin,"



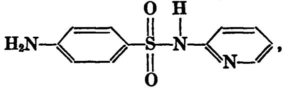
the structural basis of all the sulfonamides, is now but little used, since its derivatives surpass it in therapeutic effectiveness, and are less subject to toxic side effects, except as regards urinary crystallization. The *therapeutic dosage* of sulfanilamide should be such as to maintain fairly constantly an effective concentration in the blood, about 10 mg. per 100 cc., for serious infections. This should be checked at frequent intervals (by the method of Bratton and Marshall, 1939; J. Biol. Chem., *128:*537). The administration is generally started with 1 Gm. (15 grains) every four hours (for adults), totalling 6 Gm. per day; after forty-eight hours this is reduced to 0.5 to 0.66 Gm. every four hours, totalling 3 to 4 Gm. per day. This should be continued for some days after clinical recovery; in gonorrhea for at least two weeks. In milder infections, the daily dosage may be 3 to 4 Gm. from the start. Infants tolerate ⅓ to ½, children ½ to ¾ of the adult dose. Fluids should be restricted to 3590 cc. per day. It is customary to administer sodium bicarbonate in about half the quantity of the sulfanilamide. The absorption of the sulfanilamide is so prompt that it need not be administered parenterally except when it is not retained by the stomach. It may then be given by hypodermoclysis of a 1 per cent solution in sterilized physiologic saline solution or M/8 sodium lactate, in the same daily dose, divided into six- or eight-hour intervals. Sulfanilamide occurs as a white crystalline powder, of slightly bitter taste, sparingly soluble in water, 1 Gm. in 125 cc. Average dose, 2 Gm. *Sulfanilamide Tablets*, U.S.P., are usually available as 0.3 and 0.5 Gm.

Sulfapyrazine, 2-sulfanilaminopyrazine,



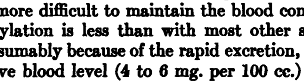
is absorbed and excreted rather slowly; the blood level rises gradually, but is easily maintained. Conjugation is relatively small. Its efficiency is similar to that of sulfadiazine; it is reported more effective against Shigella paradysenteriae. Side actions are as with other sulfonamides. Vomiting and renal injury are reported as less common. The *dosage* aims to establish its blood concentration as 5 to 12 mg. per 100 cc. The initial dose is 2 to 4 Gm., followed by 1 Gm. every four to six hours. In severe infections, *sulfapyrazine sodium* may be injected intravenously, as 5 per cent solution, starting with 0.05 Gm. per Kg. of body weight, with subsequent doses of 0.025 Gm. per Kg. in eight to twelve hour intervals. The blood concentration should not exceed 15 mg. per 100 cc.

Sulfapyridine, N.F., 2-sulfanilaminopyridine,



is already obsolescent, as its side actions are more frequent and severe and its effectiveness is rather less than with sulfadiazine or sulfathiazole. Its absorption is irregular, generally rather poor; acetylation is high, the excretion relatively slow. The blood level therefore requires close attention, preferably by chemical control, aiming at 4 to 6 mg. of free sulfapyridine per cent. Nausea and vomiting are frequent and severe; other side actions, including urinary obstruction, are about as with the other sulfonamides; dangerous complications are perhaps more frequent: acute hemolytic anemia, agranulocytosis, hepatitis. The *dosage* in pneumonia and other severe infections may start with 4 Gm., followed by 1 Gm. every four hours until the temperature has remained normal for seventy-two hours. In gonococcic infections, 3 Gm. may be given on the first day, and 2 Gm. per day, in divided doses, for the succeeding nine days. Sulfapyridine occurs as a white, crystalline, practically tasteless powder, sparingly soluble in water (1 Gm. in 3500 cc.), freely soluble in dilute mineral acids and in alkalis. *Sulfapyridine Tablets*, N.F., are usually available as 0.3 and 0.5 Gm. *Sterile Sulfapyridine Sodium* is freely soluble in water (1 Gm. in about 1.5 cc.), with strongly alkaline reaction (*p*H 10.4 to 11). It must not be used hypodermically or intramuscularly. A 5 per cent solution was employed intravenously.

***Sulfathiazole**, U.S.P., 2-sulfanilaminothiazole,



practically equals sulfadiazine in efficiency, but is more liable to toxic reactions, although distinctly less so than sulfapyridine. Its only advantage over sulfadiazine is in its lower cost. It is slightly more potent than sulfadiazine *in vitro*, but this could be adjusted by the dosage. It is rapidly absorbed, but it is also more rapidly excreted, so that it is more difficult to maintain the blood concentration. Acetylation is less than with most other sulfonamides, presumably because of the rapid excretion, so that the effective blood level (4 to 6 mg. per 100 cc.) can be attained more promptly. Nausea, emesis and dizziness are less frequent than with sulfapyridine, and mental disturbances are uncommon. Drug fever, rashes and especially scleral conjunctivitis ("pink-eye") are more frequent; blood changes and hepatitis are rare. Urinary obstruction may occur. The *dosage* for pneumococcal infections starts with 4 Gm., followed by 1 Gm. every four hours, day and night, until the temperature has been normal for seventy-two hours. For gonococcal infections, 3 Gm. may be given on the first day, then 0.5 Gm. four to six times daily for six to nine days. For *local use* in wounds, the powder may be mixed with an equal weight of sulfanilamide, to prevent clumping. Sulfathiazole occurs as a white, crystalline, practically tasteless powder, slightly soluble in water (1:1700). *Sulfathiazole Tablets,* U.S.P., are usually available as 0.3 and 0.5 Gm. *Sterile Sulfathiazole Sodium,* U.S.P., is freely soluble in water (1:2.5). It may be injected intravenously, as 5 per cent solution, starting with 0.1 Gm. per Kg. of body weight, with subsequent doses of 0.05 Gm. per Kg. in six hour intervals. The blood concentration should not exceed 12 mg. per 100 cc. Intramuscular or hypodermic injections would result in sloughing.

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PARA-AMINOBENZOIC ACID

"PABA," $C_6N_4.NH_2.COOH$, 1:4, a fairly nontoxic substance, is essential to the *growth of certain bacteria* (P. Fildes, 1940). It has been isolated from yeast, and is credited as the constituent of yeast extract which inhibits the bacteriostatic effect of sulfonamides, as discussed under that heading. *The bacteriostatic antagonism of PABA to sulfonamides* is shared quantitatively by its derivative, procaine, but not by ortho- and meta-benzoic acid (B. S. Walker and Derow, 1945). It occurs in life as well as *in vitro,* but does not extend to the toxic sulfonamide effects on animals, the fever and rash (E. Strauss *et al.,* 1941). PABA influences several metabolic oxidation-reduction systems, *catalytic reactions* which may furnish an explanation of its actions.

Para-aminobenzoic acid antagonizes the sulfanilamide inhibition of *carboxylase,* and the sulfanilamide inhibition of the *adsorption of methylene blue* on charcoal. It inhibits the destruction of *epinephrine* by *tyrosinase,* and the enzymatic oxidation of *stilbestrol.* It retards the aerobic oxidation of *tyrosine* and *dopa.* (Aniline has a similar but weaker effect; meta- and ortho-aminobenzoic acids are intermediate; Wisansky *et al.,* 1941.) It retards the action of the *luciferase* of Cypridina (F. H. Johnson and Chase, 1942).

Para-aminobenzoic acid acts as a *growth factor* for chicks, and has been included in the B complex (G. J. Martin and Ansbacher, 1941; review, S. Ansbacher, 1944), but its action is probably indirect by stimulating the intestinal bacteria to increased production of vitamins, presumably biotin and folic acid (L. D. Wright and Welch, 1943). It does not influence the growth of young rats (Ahlström *et al.,* 1943), but it sometimes cures the *gray hair* which rats develop on certain synthetic diets. This is probably also an indirect action, ascribed to better utilization of pantothenic acid. Excess of PABA also results in slight graying, attributed to increased growth of bacteria that destroy pantothenic acid (G. J. Martin, 1942). PABA prevents the syndrome of excessive inositol income (G. J. Martin, 1942).

P-aminobenzoic acid is an effective *antidote to carbarsone and certain other phenylarsonates,* as are also both its isomers, benzoic acid, phenylacetic acid and many other aromatic compounds (J. H. Sandground, 1944). The mechanism is not clear. It does not destroy the trypanocidal action of the arsonates. It is independent of the route of administration of the arsenical, but is more effective if the PABA is injected three hours in advance of the arsenic. It also protects against stibosan. It has no effect on the MLD of trivalent arsenicals, but is reported to inhibit clinical toxic reactions to these, as well as to pentavalent arsenicals in the treatment of neurosyphilis. It does not prevent nitritoid crises, gastro-intestinal reactions or optic injury (A. S. Rose *et al.,* 1944).

Louse-borne typhus fever is materially improved by intensive p-aminobenzoic acid treatment (Yeomans *et al.,* 1944), and has shown promising results in various rickettsian infections (Anigstein and Bader, 1945; tsutsugamushi disease, N.A. Tierney, 1946). The *dosage* starts with 4 to 8 Gm., then 2 Gm. every two hours, aiming to keep the blood concentration at 10 to 20 mg. per 100 cc. for at least three days, until normal temperature is maintained for twenty-four hours. Higher levels produce slight delirium (Tierney). As the free acid is irritant, it is administered as powder suspended in 25 cc. of 5 per cent sodium bicarbonate solution, followed by water. It causes no untoward effect except that the leukocyte count tends to fall, and if this drops below 3000 it should be discontinued. The mechanism of the effect on typhus is not clear, but it probably acts on the metabolism of the Rickettsias to prevent their multiplication. High concentrations check their growth in the yolk sac membrane of chick embryos (C. H. Andrews *et al.,* 1943; Greiff *et al.,* 1944).

The *prophylactic dosage* against rickettsian infections is 0.5 to 1 Gm. daily, conveniently as tablets of 0.25 Gm., with 0.65 Gm. of sodium bicarbonate per gram of PABA.

Fate.—On oral administration of 4 Gm. the plasma level rises sharply, reaching the peak in about an hour, and then falls rapidly. From 20 to 100 per cent is unconjugated in the plasma. The urine contains chiefly free p-aminobenzoate and conjugated p-aminohippurate, with smaller amounts of conjugated p-aminobenzoate and free p-aminohippurate (P. K. Smith, Bayliss *et al.,* 1946). The conjugate is chiefly acetylate, perhaps also glycuronate. Rabbits also acetylate it; dogs do not (E. K. Marshall *et al.,* 1937). *Myasthenia gravis* does not interfere with the acetylation (C. Torda and Wolff, 1944). It is *secreted by the renal tubules* so effectively that 88 per cent of its arterial concentration is removed in a single passage through the human kidneys (J. V. Warren *et al.,* 1944). Mice excrete 82 per cent within twenty-four hours; only traces remain in the organs (Lustig *et al.,* 1944). Normally, the blood, liver and kidneys contain at most a few gamma per 100 Gm. (Ahlström *et al.,* 1943).

The toxicity of p-aminobenzoic acid is low, with chronic as well as acute administration (R. K. Richards, 1942). The acute LD ($_{50}$) for various animals is 1 to 3 Gm. per Kg., orally; 2.8 to 4.6 Gm. per Kg. of the sodium salt by vein. In dogs, large doses (1 Gm. per Kg. by mouth) may produce intestinal hemorrhage; 2 Gm. per Kg. may result in acute hepatic necrosis (C. C. Scott and Robbins, 1942). S. Rothman and Rubin, 1942, claim that *in vitro* ultraviolet irradiated p-aminobenzoic acid produces a substance that sets up an inflammatory reaction when injected into the human skin.

G. R. Goetchius and Lawrence, 1947, report on the bacteriostatic and bactericidal action of a series of *N-alkyl p-aminobenzoic acid* derivatives.

Para-aminohippuric Acid, "PAHA," is excreted partly by the renal tubules and is used to estimate tubular excreting function (see Index).

PROPAMIDINE

This is an aromatic diamidine derivative, 4:4 diamidino diphenoxypropane dihydrochloride, prepared by Ewins, which arrests the multiplication of bacteria and protozoa (Lourie and Yorke, 1939), and is not inhibited by peptones and para-aminobenzoic acid (Thrower and Valentine, 1943). Local application of the 0.1 per cent solution is useful clinically in treating chronic wound infections (McIndoe and Tilley, 1943) and in burns (G. H. Morley and Bentley, 1943).

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"ANTIBIOTIC SUBSTANCES"

This name is applied to numerous chemical substances produced by living organisms, generally bacteria, fungi and actinomyces, which exert an "antimicrobic" action by interfering selectively but not specifically with the multiplication of certain micro-organisms. They occur especially in the saprophytic flora of the soil. Only a few are as yet of practical importance, notably penicillin and streptomycin.

Waksman and his associates, who introduced the term "antibiotic," found that 10 to 50 per cent of all actinomyces cultures show antibiotic activity, often very great, but differing widely in scope. Some are effective against only a few varieties, others have a wide field. The therapeutically useful antibiotic agents are highly specific. Gram-positive organisms are more susceptible than are gram-negative ones. The production of the antibiotic agent depends on the strain rather than on the genus or even species.

A species often produces several such substances; for instance, *Penicillium notatum* also furnishes *penatin*, reported to be a more potent bacteriostatic than penicillin. Aspergillus fumigatus of stable manure yields four antibiotic agents. On the other hand, the same substance, for instance *clavacin*, may be produced by different organisms (review, S. A. Waksman, 1944).

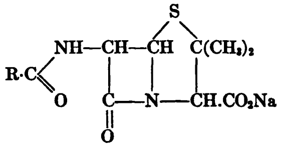
Penicillin and streptomycin are rapidly excreted, and have a low toxicity for animals. They act primarily on bacteria, but little on virus, and practically not on fungi. Penicillin is effective especially against cocci, gram-positive aerobes and anaerobes and against spirochetes. It has little effect on gram-negative and acid-fast bacteria. *Streptomycin* is effective against both gram-positive and gram-negative and acid-fast bacteria, relatively less against cocci, spirochetes and anaerobes.

These two agents also differ in facility of developing resistance, and resistance acquired to the one does not extend to the other (review, Waksman, 1947).

PENICILLIN

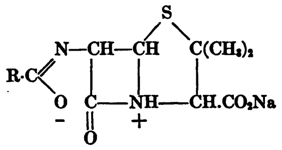
Penicillin is an outstanding "antimicrobial agent," producing successively, with increasing concentrations, arrest of growth, death and disintegration of susceptible bacteria, fungi, protozoa and other micro-organisms. It is used to overcome infections on the principle of arresting multiplication of the parasites, presumably by interfering with their metabolism, rather than by killing them outright. This is fundamentally analogous to the action of sulfonamides. The bacteriostatic action of penicillin was discovered by A. Fleming in 1929; its therapeutic application originated with Chain, Florey *et al.*, 1940 (history, L. A. Falk, 1944). It was originally prepared as progressively purified extracts from cultures of a special strain of the mold *Penicillium notatum.* Its synthesis has been accomplished by du Vigneaud, Carpenter *et al.*, 1946, but not in commercial quantities. Four varieties of penicillin, designated as F, G, K and X, have been isolated from the same mold, their quantities differing with cultural conditions. They are esters of a substance which probably has one of the following formulas (Med. Res. Com., 1945, Science, *102:*627):

(I)



or:

(II)



In G penicillin, R stands for benzyl, in X for p-hydroxybenzyl, in F for Δ^2-pentenyl, in K for n-heptyl. They are strong monobasic acids and are marketed as somewhat impure calcium or sodium salts which are readily soluble in water.

Dilutions of 1:50,000,000 completely inhibit the growth of susceptible bacteria, while other varieties, for instance the tubercle bacillus, are quite resistant. In general, gram-positive bacilli and gram-negative cocci are susceptible, and gram-negative bacilli are insusceptible, but the strains may differ more than the species. The action is not significantly impaired by blood or pus or by the number of bacteria. Penicillin is not hemolytic, and is remarkably nontoxic to body tissues, including tissue cultures. Its clinical use against susceptible forms is spectacularly effective, supplementing and overlapping the sulfoniamides and supplanting them to a considerable degree because of its nontoxicity as well as its potency. Oral administration can be made effective, but is wasteful, since it is rather poorly and capriciously absorbed from the gastro-intestinal tract and is rapidly excreted. It is best administered by intramuscular or intravenous drip instillation, to maintain effective concentrations. It is not toxic to animals in concentrations hundreds of times greater than are needed for bacteriostasis.

Preparation.—Penicillin is obtained by growing special strains of the Penicillium mold on suitable media for an optimal time. The culture fluid contains more than the felt of mold, and is extracted with differential solvents and dried. It must be preserved in a vacuum, as it is *readily destroyed,* especially when it contains moisture. The decomposition of crystalline sodium penicillin in solution is autocatalytic, and if once started it is difficult to control. Its rapidity increases with temperature (B. Berk *at al.,* 1947). Solutions of crystalline penicillin G lose their potency more rapidly than the purified. The decomposition is retarded by small amounts of phosphate, 0.005 M (R. Pratt, 1947). Commercial penicillins before 1944 contained chiefly G or mixtures of G and F. Then changes in manufacture decreased the G considerably, with increase of F and especially K. There is little of X in most. Purification has increased the potency from 200 units to the current level of 900 to 1400 units per milligram (Com. Med. Res. 1946, J.A.M.A., *131:271*). The varieties differ somewhat in potency *in vitro,* and much more so *in vivo.* The X is considerably more potent against most bacteria, including gonococcus. It also maintains its blood concentration better with intramuscular injection, so that smaller doses suffice (Libby and Holmberg, 1945; Ory *et al.,* 1945). K is so rapidly destroyed in the body that its therapeutic efficiency is much weaker; for instances, in experimental syphilis (Eagle and Musselman, 1946; Heller, Moore *et al.,* 1946).

Esterification of the carboxyl group of penicillin greatly increases the stability (K. Mayer *et al.,* 1943). *Benzyl penicillin* is at least three times as potent as sodium penicillin (C. J. Cavallito *et al.,* 1945).

“*Penicillin B*” is an entirely different substance, a flavoprotein which oxydizes glucose to gluconic acid and hydrogen peroxide. Through the latter, it is a highly effective bacteriostatic, but it is toxic (E. C. Roberts *et al.,* 1943; van Bruggen *et al.,* 1943).

The *penicillin unit* is used to assay the penicillin preparations and to express the dosage. The present international unit is 0.6 micrograms of pure crystalline sodium penicillin G (A. C. Hunter, 1944; P. Hartley, 1945); 100,000 units would correspond to 60 mg. of the pure penicillin salt, and 1 mg. would contain 1667 units. This unit is close to the older *Oxford* (Florey) *unit,* “that amount of penicillin which, when dissolved in 50 cc. of meat extract broth, just inhibits completely the growth of the test strain of staphylococcus aureus.” *In vitro,* 0.03 unit per 100 cc. suffices to sterilize all susceptible bacteria except some strains of meningococcus and staphylococcus, which require 0.06 to 0.24 units; some staphylococci require more (Finland *et al.,* 1945).

Fate.—Penicillin is distributed freely through all fluids and tissues except the nervous system. The major portion is excreted in the urine (about 60 per cent with intravenous, 14 per cent with oral, administration; A. H. Free *et al.,* 1945); minor fractions by the bile and saliva. The fate of the remainder is not known. It is not rapidly destroyed in the blood *in vitro* at body temperature (Cutting, Ludueña *et al.,* 1945).

Absorption of orally administered penicillin varies with the individual and with conditions, but is always incomplete. Effective doses can be given, but with considerable waste. It requires generally five times as much as with intramuscular injection to maintain an equal blood concentration. The absorption occurs chiefly from the duodenum and takes place promptly, reaching the maximum blood level in half an hour to one hour after ingestion, but about two-thirds are not absorbed, presumably because they pass beyond the absorbing area. The unabsorbed penicillin is destroyed by the intestinal bacteria or escapes in the feces. A small amount is inactivated by the gastric acidity. The effect is therefore somewhat greater if it is administered when the stomach is not acid, fasting, or still better in patients with achlorhydria; but not more than a third is absorbed even in the entire absence of acid (W. McDermott *et al.,* 1946). Buffering with alkali is but little better than simple saline; aluminum hydroxide protects somewhat better, but not much (M. Finland *et al.,* 1945; J. Charney *et al.,* 1945). Enteric-coated capsules give absorption similar to that in achlorhydria, but are far inferior to intramuscular injection (L. D. Seager, 1946). Even when penicillin is placed directly in the intestines, its absorption is poor and variable. In the rectum it is destroyed by some of the fecal bacteria. *Vaginal absorption* of penicillin is quite good, except near the end of gestation (J. Rock *et al.,* 1947).

Distribution.—The concentration of penicillin in the blood reaches its peak within thirty minutes after *intramuscular or hypodermic injection,* remains moderately high for an hour and falls rapidly in the second hour, persisting at lower levels for three or four hours (J. V. Cooke and Goldring, 1945). The concentration falls to almost nothing within an hour after *intravenous injection.* It passes promptly into the urine and extracellular fluids; the concentration in the pleural and peritoneal fluid, and in the joint fluid in rheumatoid arthritis, approximates that in the blood. The concentration in the *red blood cells* is less than a tenth of that in the plasma (Rammelkamp and Keefer, 1943). It passes through the human *placenta* so as to raise the titer of the fetal blood considerably above the bacteriostatic level (H. J. Greene and Hobby, 1944). It is not excreted into bovine *milk* (Seeley *et al.*, 1945). It passes into the fluids of the *eye* promptly, but in small amount. Subconjunctival injection or constant corneal bath attains high concentrations in the ciliary body, moderate in the humors (Struble and Bellows, 1944). The concentration in the *cerebrospinal fluid* is materially less than in the blood, but reaches therapeutic levels (to 0.55 units per cubic centimeter) with intravenous injection of 10 to 25 million units, but is capricious. There is practically none with intramuscular injection of 500,000 units (Schwemlein *et al.*, 1946). Intrathecal injection of a large therapeutic dose keeps the concentration high for twenty-four hours, and passes readily into the cerebral meninges. It produces various degrees of meningeal irritation, but not sufficient to preclude its use (Rammelkamp and Keefer, 1943; Cooke and Goldring, 1945).

The level in the plasma is lower for K than for G. Both are partly bound in by plasma protein, K much more than G. With continuous infusion, G and K accumulate in the liver, kidneys and lungs in higher concentration than that of the plasma. K differs from G by relatively greater accumulation in the liver and less in the lungs (A. P. Richardson, 1947). Serum albumin antagonizes the potency of the four penicillins in different degree, proportional to the degree of binding (R. Trumpsett *et al.*, 1947).

The *excretion of penicillin* occurs rapidly by the urine. On intravenous injection, half to two-thirds are excreted within an hour; most of the remainder is destroyed in the body, possibly in the liver. With oral administration the urinary excretion is considerably less, 8 to 33 per cent of the dosage, because of the gastro-intestinal destruction (A. H. Free *et al.*, 1944). In renal insufficiency, the concentration in the blood and cerebrospinal fluid stays considerably higher (J. V. Cooke and Goldring, 1945). The *renal clearance* of K, G and X penicillin in man normally approximates the total renal plasma flow, being about equal to the clearance of parahippuric acid, and four or five times that of inulin or thiosulfate. It is independent of the blood level and of the rate of urine flow, and could be used to test renal plasma flow and function. The clearance of K penicillin is only a fourth to a half that of G, F or X, perhaps by inactivation in the kidneys (H. Eagle and Newman, 1947).

Glomerular filtration and tubular excretion both participate in the urinary elimination of penicillin. In man, about 20 per cent of the output is glomerular, 80 per cent tubular. Blockage of the tubular secreting mechanism by intravenous injection of 30 cc. of diodrast solution decreases the urinary excretion route by half and the blood level falls correspondingly slowly (Rammelkamp *et al.*, 1943). A similar blockage is produced by the less toxic *p-aminohippuric acid*, "PAHA." The "PAHA" is excreted so rapidly that 88 per cent is removed from the blood by a single passage through the human kidney circulation. With continuous intravenous injection in dogs, 78 to 92 per cent is excreted in the urine; with oral administration, 55 per cent in the urine and feces (K. H. Beyer, Mattis *et al.*, 1946). These agents are excreted by the same tubular mechanism, and higher concentrations block the tubular excretion of penicillin by "main action," probably by substrate competition; but the necessary doses are too high for clinical use (K. H. Beyer, 1947). With moderate doses, the only untoward reactions consist in contraction of the large intestine and bladder, without discomfort (K. H. Beyer *et al.*, 1944; Finkelstein *et al.*, 1941; J. V. Warren *et al.*, 1944). Very large intravenous injections of the sodium salt into dogs, at plasma concentration of 0.6 Gm. per cent, produce widespread passive congestions and edemas, focal necrosis of the liver, and toxic nephrosis (P. A. Mattis, Beyer *et al.*, 1945). *Benzoic acid* has a similar effect (four capsules of 0.6 Gm., or in orange syrup, with restriction of water and sodium chloride intake; Bronfenbrenner and Favour, 1945).

Caronamide, 4'-carboxyphenylmethane sulfonalide, also blocks the tubular excretion of the penicillins, presumably also by competing for the substrate, although it is not itself excreted by the tubules. Much smaller doses therefore suffice to increase the plasma level of the penicillins materially. The action is reversible, apparently without ill effects. It is effective by mouth and parenterally (K. H. Beyer, 1947). Its clinical use is in the experimental stage.

The mechanism of the penicillin action and of the different susceptibility of various bacteria is not known (review, C. N. Frazier and Frieden, 1946). In general, the bacteriostatic action is parallel to the concentraton, *in vivo* and *in vitro;* but the minimal effective concentration, 1:50,000,000 for gonococcus, is of the order of magnitude of enzymatic reactions. Presumably it interferes with enzymatic processes essential to the multiplication of bacteria, acting on the fission rather than on the growth (E. Chain and Duthie, 1945). Antibiotic substances in concentrations that do not effect complete inhibition tend to produce extreme elongation of the cells by preventing division (A. D. Gardner, 1940). Electromicrographs indicate that it inhibits and kills the vulnerable bacteria without preceding cellular changes, resembling sulfonamides and gramicidin (L. J. Weiss, 1943). Penicillin does not cause lysis of the bacteria, as does bacteriophage (review, Schmitt, 1944). It appears to protect mice to a considerable degree against the lethal action of *endotoxins* of certain gram-negative bacteria, for instance meningococcal and gonococcal. The mechanism is not understood (A. K. Boor and Miller, 1945; G. Ramon *et al.*, 1946; C. P. Miller, Boor and Hawk, 1947).

Penicillin is inactivated by various *sulfhydryl compounds*, including thioglycolic acid and cysteine, suggesting that it interferes with the function of sulfhydryl groups in the normal bacterial metabolism (Cavallito and Bailey, 1944). *Amino acids* generally antagonize the penicillin action against gram-negative bacilli, and this may explain the natural resistance of this group. Methionine, threonine and methionine sulfoxide greatly increase their susceptibility (G. Shwartzman, 1946). The bacteriostatic action is destroyed by *diastatic ferments*, taka-diastase, 1:200, or "*clarase*," 1:4000 (C. A. Lawrence, 1943).

Ordinary penicillin inhibits the *germination of seeds*. This is due to contamination with indole-3-acetic and phenylacetic acid. Pure penicillin has no effect on germination (W. J. Smith, 1946).

Resistance to penicillin develops in bacterial subcultures subjected to gradually increasing concentrations, and may reach 6000 times the normal, with corresponding decrease of virulence (C. M. McKee and Houck, 1943), but a considerable degree of virulence may be retained (C. P. Miller and Bohnhoff, 1945). The resistance is due to selection by survival of the more resistant individuals (M. Demerec, 1945), which perhaps avail themselves of substitute metabolic mechanisms that are not inhibited by the antibiotic agent (Waksman, 1947). The resistance also develops in the bacteria if patients are subjected to insufficient penicillin treatment, and becomes a fairly stable hereditary quality (L. H. Schmidt and Sesler, 1943). It does not alter the susceptibility to sulfonamides, and vice versa (H. M. Powell and Jamieson, 1942). Certain bacteria and molds develop an enzyme, *penicillinase*, which destroys penicillin (E. P. Abraham and Chain, 1940), but this is not the mechanism of tolerance (A. Bondi and Dietz. 1944).

Untoward reactions are rather infrequent and mild. No fatalities or very serious toxic effects have been reported clinically, and its toxicity for animals or excised tissues is low (W. Cutting *et al.*, 1945). Many of the milder reactions were attributable to impurities and are decreasing as the commercial product is becoming purer. They may, however, occur with the crystalline product, which may sometimes produce sensitization (review, C. J. Lyons, 1943; Schmitt, 1944)

Local irritation varies with the purity, but even the purer commercial penicillins may cause transient burning *pain* at the site of intramuscular injection (R. P. Herwick *et al.*, 1945). *Thrombophlebitis* may occur if the same vein is used too long for intravenous injections. Mild *nitritoid reactions* are sometimes seen during intravenous administration. *Early reactions,* generally rashes and edemas, may occur in 16 per cent of the patients, especially in dermatologic patients. Delayed reactions, especially *urticaria* and *pruritus*, develop one or two weeks after starting penicillin therapy, in about 7 per cent of the patients, not materially more in dermatologic cases (Kolodny and Denhoff, 1946). They do not prohibit further administration, since they tend to subside within five days, even if the injections are continued. A few patients develop symptoms of serum sickness, with effusion into the joints and exfoliative dermatitis, but they recover spontaneously in seven to ten days (E. J. Gordon, 1946). Some cases of peripheral neuritis are reported after intramuscular injection of penicillin, the majority with complete recovery (L. C. Kolb and Gray, 1946).

The *coagulation time* is markedly shortened after clinical use of penicillin (L. F. Moldavsky *et al.*, 1945).

It is not known whether the reactions are due to penicillin proper, or to impurities. The pain and dermatitis vary with the samples. They are generally much less in the purer drug, and are not parallel to the therapeutic efficiency (review, H. Molitor, 1946). The urticaria and angioneurotic edema suggest allergy, especially as they respond to epinephrine and ephedrine. Commercial penicillin produces anaphylactic sensitization in guinea pigs (McClosky and Smith, 1944), but the clinical reactions show no significant relation to previous penicillin therapy or to past allergic history (Kolodny and Denhoff, 1946). W. C. Chu and Cutting, 1946, demonstrated mild local sensitization of the Arthus type in man and in animals, with pure as well as with commercial penicillin. Old healed mycotic lesions may react to penicillin (J. H. Lamb, 1943), and the higher frequency in dermatologic patients may be due to residual fungi.

Muscular cramps, tingling of the testes and *eosinophilia* may occur. *Chills* and *fever* may accompany the urticaria, but are infrequent since the preparations are tested for absence of pyrogens.

Direct application of 500 units of crystalline penicillin to the *cerebral cortex* of dogs and monkeys produces convulsive movements, probably due to the penicillin itself, since it parallels the antibiotic potency (A. E. Walker and Johnson, 1945). The threshold in man appears to be considerably higher, much above the therapeutic level (H. C. Johnson, Walker *et al.*, 1946). Streptothricin, streptomycin, clavacin and actinomycin also produce these effects (A. E. Walker *et al.*, 1946). The acute and chronic *toxicity for rodents* is reported by Hamre *et al.*, 1943, and by H. J. Robinson, 1943. It varies for different samples and has no relation to the therapeutic potency (review, H. Molitor, 1946). It is much more toxic for guinea pigs than for man and many other animals (Heilman and Herrell, 1944).

Therapeutic Uses.—Penicillin is employed especially in pneumococcus pneumonia, staphylococcus septicemia, gonococcus infections, meningitis, thoracic empyema, bacterial endocarditis, osteomyelitis and other serious infections of organisms susceptible to it, and in agranulocytosis.

In *gonococcal urethritis,* penicillin appears to be the most successful treatment, and its nontoxicity is an added advantage. The chief objection is that it masks the usual development of acute syphilis and so interferes with diagnosis; secondary syphilis following penicillin therapy is reported by D. W. Atcheson, 1945. Penicillin is also ineffective against chancroid and lymphogranuloma venereum.

The gonococcus is the most sensitive of all organisms to penicillin; 85 to 98 per cent of urethral infections are curable by penicillin alone. Successful results in gonorrheal arthritis are reported as somewhat less, 58 per cent, ascribable largely to errors of diagnosis. Resistant strains have not been encountered (review, Hench, 1946).

Acute and chronic gonococcus infections respond with remarkable rapidity to penicillin treatment. Definite improvement, both as to symptoms and bacterial count, is noticeable in two to five hours after an intramuscular injection, and these usually completely clear within forty-eight hours. With the penicillins now on the market, satisfactory results may be expected with a total dosage of 200,000 units (four hourly intramuscular injections of 50,000 units), even with ambulatory patients (J. R. Heller, 1946), and those resistant to sulfonamides (G. J. Thompson, 1944); indeed, a single intramuscular injection of penicillin X may suffice (H. Welch *et al.*, 1944).

Syphilis in its early stages yields well to intensive penicillin treatment. This effects the clinical and serological cure as satisfactorily as intensive arsenic therapy, with much greater safety. Relapses are rare and in inverse relation to the total dose. The dosage used for gonorrhea is quite inadequate and merely obscures the early symptoms (B. Shafer and Zakon, 1944).

Dosage Schedule for Early Syphilis.—Aqueous injections of penicillin sodium should be administered intramuscularly every two or three hours day and night for at least seven and a half days. For serum-negative cases the total should be not less than 3,600,000 units, *i. e.*, 90 injections of 40,000 units every two hours, or 60 injections of 60,000 units every three hours. For serum-positive cases, the total should be not less than 5,400,000 units, *i. e.*, 90 injections of 60,000 units every two hours or 60 injections of 90,000 units every three hours. In case of relapse of early syphilis, the course must be repeated, and, in addition, with 60 mg. of oxophenarsine hydrochloride intravenously two or three times weekly, to a total of six injections (360 mg), together with intramuscular injections of 0.2 Gm. of bismuth subsalicylate twice a week for six doses (totalling 1.2 Gm.). In case of a second relapse, the treatment should be changed from penicillin to the arsenic and bismuth routine. In *later or latent syphilis* of adults, the dosage of penicillin should total not less than 3,600,000 units; in *paralytic dementia* not less than 10 million units, divided over twelve to fifteen days. It may be joined with fever therapy. Oral administration of penicillin against syphilis is not justified. The suitability of beeswax oil suspension is not decided (Com. Med. Res., 1946, J.A.M.A., *131:265*).

Experience with experimental syphilis in rabbits illustrates that relatively small doses of penicillin suffice to abort the infection, and that the dosage must be much increased, progressively, as the infection becomes established (H. Eagle, Magnuson and Fleischman, 1947).

The response in early syphilis is immediate and profound, with disappearance of the organisms from open sores, healing of the lesions and a trend toward serologic reversal. Herxheimer reactions (hyperpyrexia) are frequent, but not sufficiently serious to interrupt the treatment (J. E. Moore *et al.*, 1944). Very early infections respond most favorably; infections that have lasted two months or longer give twice as many failures as those treated in the first week (Com. Med. Res., 1946, J.A.M.A., *131:265*); some cases appear relatively resistant, and some are practically failures (J. F. Mahoney *et al.*, 1944). The immediate results are as good from the minimal effective dosage as from much larger doses, but the relapses occur in inverse ratio to the dosage and to the length of administration (W. McDermott *et al.*, 1945). Failures within eleven months after treatment are four times as frequent with 600,000 than with 2,400,000 units (62 per cent against 15 per cent). The addition of oxophenarsine or bismuth reduces the failures by half (Com. Med. Res., 1946, J.A.M.A., *131:265*). With the above dosage, nearly all patients are seronegative twelve to twenty months after the treatment (W. Leifer, 1945). The proportion of failures appears to have increased with the purification of the penicillin, suggesting that the antisyphilitic action is due in large part to some impurity (W. B. Dunham and Rake, 1945), but this may not be the explanation; it may be the preponderance of penicillin K. H. Welch, Randall and Price, 1947, report a "factor" in many commercial penicillins which enhances the effectiveness of pure penicillin, without having any effect by itself.

The antispirochetal potency of penicillin can be rapidly appraised by experimental infection with Borrelia novyi (Buck, Farr and Schnitzer, 1946).

In *late syphilis* the results are also good. The abnormal spinal fluid is improved in most. Benign gummas, skin, bone and vascular lesions heal in twelve to sixty-four days with the dosage of 300,000 units. Oxophenarsine and bismuth may be given concurrently.

Syphilitic pregnant women should be treated with penicillin in the same dosage as for early syphilis, in preference to metals. Children born under this treatment are free from syphilis (Stokes *et al.*, 1944; Ingraham *et al.*, 1946; Goodwin and Moore, 1946). *Infantile syphilis* gives about 70 per cent success with 64,000 units per pound, spread over seven to fifteen days; larger doses might give better results (Ingraham *et al.*, 1946; Platou *et al.*, 1945).

Neurosyphilis is more or less improved in early and late cases; two courses of larger doses are recommended (G. H. Gammon *et al.*, 1945). The most striking effect is on the spinal fluid formula, which shows definite improvement in about 71 per cent and becomes nearly or quite normal in 36 per cent, with corresponding clinical improvement. The spinal fluid cell count, protein and gold curve return to normal. The serum reaction turns toward normal; severity of leg pains is decreased; dementia is at least improved. Meningeal neurosyphilis responds much better than does parenchymatous. The greatest improvement is in the first 120 days, and this is not materially increased by repeating the course. Relapse may occur, but rarely to the original severity (Stokes, Steiger *et al.*, 1946). Penicillin does not increase the response to fever therapy (P. A. O'Leary *et al.*, 1946).

In *agranulocytosis*, penicillin is used to prevent infection, in preference to sulfathiazole, which is also effective, but may itself produce decrease of granulocytes; penicilllin does not affect them. The dosage should be 1,000,000 units or more daily (E. W. Boland *et al.*, 1946).

Indications for penicillin depend chiefly on the susceptibility of the infecting organisms. They may be placed in four groups (following essentially Keefer *et al.*, 1945).

Group I: Effective.—All infections by staphylococci, clostridia, hemolytic streptococci, anaerobic streptococci, pneumococci, gonococci, anthrax (F. D. Murphy *et al.*, 1944); chronic pulmonary suppurations in which surgery is contemplated; meningococcal infections that fail to respond to sulfonamides; bacterial endocarditis due to susceptible organisms; erysipeloid infections; Vincent's infections; prophylaxis against secondary infections as tonsillectomy; or tooth extraction on patients with history of rheumatic fever. Penicillin is also used in treating certain diseases of plants (J. G. Brown and Boyle, 1944). In scarlet fever, penicillin is about as effective a convalescent serum, and more so than sulfonamides. It produces prompt fall of temperature, decreases the toxicity and secures a smaller incidence of pyogenic infections (H. L. Hirsh *et al.*, 1947; A. L. Hoyne and Brown, 1947).l

It is now considered as specific against the tropica spirochetal diseases, yaws, pinta, relapsing fever and leptospirosis (review, E. C. Faust, 1946).

Group II: Effective, but Requiring Additional Experimental Work.—Syphilis, actinomycosis, diphtheria in conjunction with antitoxin, psittacosis in mice, Weil's disease in guinea pigs (Heilman and Herrell, 1944).

Group III: Questionable Value.—Mixed infections with predominant gram-negative flora.

Group IV: Ineffective.—All gram-negative bacteria, such as H. influenzae, typhoid, dysentery, colon, pyocyaneus, Friedländer's bacillus, undulant fever, tularemia, Klebsiella pneumonia, tuberculosis, toxoplasmosis, histoplasmosis, acute rheumatic fever (R. F. Watson *et al.*, 1944; F. P. Foster *et al.*, 1944); lupus erythematosus, infectious mononucleosis, pemphigus, Hodgkin's disease, leukemia, ulcerative colitis, coccidioid mycosis, malaria, poliomyelitis, blastomycosis, monilia, virus infections, cancer.

Synergism of penicillin and sulfonamides is marked *in vitro*, but clinical data are inadequate (Rammelkamp and Keefer, 1943). The effectiveness of penicillin is greatly increased by *hyperthermia* (on spirochetes *in vitro*, Eagle and Musselman, 1944; on bacteria, S. W. Lee and Foley, 1944).

The *dosage* should aim to bring the infection under control as rapidly as possible; this also diminishes the hazard of inducing fastness. The daily dose is usually between 40,000 and 100,000 units, and up to 240,000 units. The rapid elimination requires a continuous supply, day and night, to maintain adequate blood concentration, generally about 0.5 to 0.3 units per cubic centimeter. This may be accomplished (1) by intravenous injection of 15,000 to 20,000 units, followed by intravenous drip instillation of 2000 to 5000 units per hour; or (2) it may be approximated by intramuscular injection of 10,000 to 20,000 units every two to three hours (Florey and Florey, 1943); or effectively but rather wastefully by oral administration of about four times the intramuscular dose every three to five hours. Hypodermic injection is painful and should not be employed. The penicillin may be discontinued when the temperature is normal.

The range in which organisms in cultures succumb to penicillin is quite narrow, about a decimal. The therapeutic efficiency depends on keeping within this range continuously for a considerable time. Lower concentrations would be ineffective, higher would be superfluous. Larger doses would not increase the action; they would only prolong it (H. Eagle, 1947).

Preparation of Solutions.—Penicillin is marketed as the partly purified dry calcium or sodium salt, in vacuum-packed vials or ampuls of 25,000 and 100,000 units. It is quickly soluble, and its solutions deteriorate rapidly. It is dissolved at the time of injection in sterile pyrogen-free distilled water or isotonic salt solution, or 5 per cent dextrose solution, in the following ratios: for intravenous injection with syringe, 1000 to 5000 units per cubic centimeter; for continuous intravenous injection, 25 to 50 units per cubic centimeter; for intramuscular injection, 5000 units per cubic centimeter; for intrathecal injection, 1000 units per cubic centimeter; for local application, 250 to 500 units per cubic centimeter. Solution not used immediately should be kept in a refrigerator, preferably not longer than twenty-four hours and never longer than forty-eight hours. It loses in potency, but does not become toxic.

Irritation from intramuscular injection is materially greater with some lots than with others. Intragluteal injections produce least pain (R. P. Herwick *et al.*, 1945).

Prolongation of the action to about double the ordinary duration of injected penicillin may be secured (1) *by blocking the excretion through the renal tubules* with diodrast or p-aminohippuric acid or benzoic acid (see under Excretion); and (2) *by slowing absorption from intramuscular injections* by applying an icebag to the site (Trumper and Hutter, 1944); or by injecting epinephrine (R. T. Fisk *et al.*, 1945); or by adding 6 to 20 per cent of gelatin (W. M. Parkins *et al.*, 1945); or by suspending the penicillin in peanut oil containing 1 to 6 per cent of beeswax. A single intramuscular injection with this medium often suffices to cure gonorrhea (Romansky and Rittman, 1944).

Oral administration of penicillin was at first discouraged as wasteful of the limited supply. This no longer holds, especially as the same degree of purification is not necessary. The blood level is perhaps somewhat less predictable than with parenteral injection, but therapeutically effective concentrations can be obtained and maintained in pneumonia as well as in gonorrhea (Finland *et al.*, 1945; P. A. Bunn *et al.*, 1945) by the oral administration of 100,000 units five times per day, taken fasting, in watery solution, or in tablets or capsules of 20,000 units. The blood concentration rises somewhat higher, but not significantly so, if an alkali buffer is taken at the same time: sodium citrate, 1 to 5 Gm. for each dose, or disodium phosphate, 2.5 Gm., in a tumbler of water (P. György *et al.*, 1945; Charney *et al.*, 1945); or somewhat better with a tablespoonful of aluminum hydroxide cream (A. L. Barach *et al.*, 1945). Suspension in oil (R. L. Libby, 1944) does not appear of material advantage (W. McDermott *et al.*, 1945). *Theobroma suppositories* with sodium penicillin are reported by L. Loewe *et al.*, 1945, to produce effective levels, but absorption from rectal instillation is poor.

Intrathecal spinal injections of 10,000 units in 10 cc. of saline solution, once or twice daily, are used in meningitis to supplement systemic administration, since the latter alone attains only low concentrations in the cerebrospinal fluid. They are harmless, although there may be some headache (Rammelkamp and Keefer, 1943).

Local injection of 20,000 to 40,000 units, diluted to 5000 units per cubic centimeter of saline, may be made into pus cavities, empyema and joints, after aspirating the pus. In brain abscess, the dilution should be 1000 units per cubic centimeter. There is considerable absorption of penicillin from these situations, so that a single injection of 120,000 units renders the blood bacteriostatic for twenty-four hours, or for forty-eight hours with 240,000 units (M. E. Florey and Heatley, 1945).

Aerosol of calcium penicillin, 0.5 to 1 cc. containing 25,000 to 50,000 units, inhaled as a mist, is useful in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess (A. L. Barach, 1945). Penicillin mist is rapidly absorbed through the respiratory mucosa, giving blood concentrations intermediate between intramuscular and intravenous injection (Mutch and Rewell, 1945).

Topical application may be made by compresses saturated with 250 to 500 units in saline; or by *ointment* of calcium penicillin containing not less than 250 units per gram, never by penicillin in substance. *Troches*, with not less than 500 units, may be used in Vincent's angina. Penicillin *dental cones* are inserted into the socket after tooth extraction.

PREPARATIONS.—***Penicillins** are marketed as the partly purified sodium or calcium salt. They must comply with the requirements of the Federal Food and Drug Administration, and all specimens are checked for sterility, toxicity and pyrogen (Keefer, Herwick *et al.*, 1945). They occur as a yellow or brown powder, put up in airtight vials or ampuls. They are fairly stable, but deteriorate slowly, especially if the temperature s warm; they should be stored in a refrigerator. They are very soluble in water, and the solution loses rapidly in potency. The calcium salt is the more stable, and is equally satisfactory in every other respect. Dry crystalline penicillin is stable.

Commercial penicillin contains chiefly F, G and K; crystalline, chiefly G as sodium or potassium salt. When labeled as G, it must contain at least 90 per cent of G and have a potency of at least 1500 units per milligram. Penicillin for parenteral or oral use must not contain more than 30 per cent of the K variety.

***Penicillin Cal ium,** U.S.P., "the calcium salt of an antibiotic substance produced by the growth of Penicillium notatum or chrysogenum, or produced by other means."—*Penicillin Calcium for Injection,* U.S.P. Its potency must be not less than 500 units per milligram, except when it contains not less than 90 per cent of the salt of penicillin X, when its potency must be not less than 350 units per milligram. Average intramuscular dose, 300,000 units. *Penicillin Calcium for Oral Use,* U.S.P., contains not less than 300 units per milligram. Average dose, 300,000 units, fasting.

Penicillin Sodium, U.S.P. Potency requirement as for the Penicillin Calcium.

Penicillin Injection in Oil and Wax, U.S.P., is a suspension of penicillin calcium in a menstruum of vegetable oil in which white wax has been dispersed. Usual sizes, 100,000 and 200,000 and 300,000 in 1 cc. *Penicillin Tablets,* U.S.P., penicillin calcium or sodium, buffered with calcium carbonate, sodium citrate, aluminum hydroxide or other buffers. Usual sizes, 20,000 and 25,000 units. *Penicillin Troches,* U.S.P., contain penicillin calcium or sodium; usual sizes 500, 1000 and 20,000 units. *Penicillin Dental Cones,* and *Penicillin Ointment,* U.S.P., contain penicillin calcium.

STREPTOMYCIN AND STREPTOTHRICIN

These are soluble, thermostable nitrogenous bases found by Waksman *et al.*, 1943, in species of streptomyces (streptothricin in S. lavendulae; streptomycin in S. griseus), soil micro-organisms (actinomycetes) related to bacteria and fungi. They are bacteriostatic to both gram-positive and negative bacteria. Streptomycin, which has been isolated as crystals, contains guanidine as one of its functional groups (H. E. Carter *et al.*, 1946). Streptothricin has a delayed toxic action on animals, but streptomycin is practically nontoxic on hypodermic injection. Its clinical scope is under trial, especially in nonspecific urinary infections (H. F. Helmholz, 1945). Its antisyphilitic potency is only 1/3000 that of penicillin (W. B. Dunham and Rake, 1946). Even high doses are only moderately effective and do not prevent relapses (Herrell and Nichols, 1945). It suppresses but does not eradicate experimental tuberculosis in guinea pigs (W. H. Feldman *et al.*, 1945). It is more effective than promin, and the best results are obtained by using them together (M. I. Smith and McClosky, 1945). In human tuberculosis it appears to be somewhat bacteriostatic, but the results are not so good as in animals. It promises to be a useful adjuvant to other methods of treatment, however. Large doses continued for several months appear to arrest the progress, and this gives opportunity for therapeutic intervention. These doses, however, generally develop some toxic manifestations (H. C. Hinshaw and Feldman, 1947). Untoward reactions are not infrequent (10 per cent) with ordinary doses, but are generally mild and clear promptly on discontinuing the medication, but this is rarely necessary (L. L. Terry, 1947).

Therapeutic Scope.—Keefer, Blake *et al.*, 1946, conclude that streptomycin has proved *most effective* against tularemia, Hemophilus influenzae, urinary infections by gram-negative bacteria, and gram-negative bacteremias and meningitis. It has proved *disappointing* against typhoid, brucellosis and Salmonella. It is *under trial* in peritonitis, gram-negative pulmonary infections and tuberculosis.

Urinary Tract Infections.—Streptomycin is the most effective agent against gram-negative bacteria. At least 0.8 Gm. should be injected daily, and the urine kept alkaline. It should be continued for three days. The urinary bacteria develop fastness rapidly, and to a high degree, and if the infection is not materially improved in five days, they have probably become refractory and further administration is useless (G. T. Harrell, 1947).

Tuberculosis.—Streptomycin inhibits the growth of Mycobacterium tuberculosis in animals and in man, and so arrests the progress of the disease, although this is not eradicated. These bacteria do not become resistant to the drug till two to four months, giving opportunity for therapeutic results. Clinical improvement is demonstrable in various types of tuberculosis, but the improvement is limited and often not permanent. Large doses must be administered over long periods, 1 to 3 Gm. daily for at least two to four months, a total of 360 Gm. These large amounts generally produce toxic manifestations, especially impaired function of the eighth nerve. Careful laboratory control is necessary. W. McDermott, Muschenheim *et al.*, 1947, report definite and sometimes dramatic effects in all of their forty-one patients, with rapid fall of temperature, symptomatic improvement, and regression of the lesions demonstrable by x-ray. P. A. Bunn, 1947, reporting on ninety patients in Veterans Administration hospitals, found that none became worse or developed new lesions under the treatment; and none was completely cured. Exudative lesions showed the greatest improvement. Streptomycin appears to heal some lesions, and to serve as an adjuvant to other measures. Its field is probably to supplement rather than to displace these.

Leprosy.—Some encouraging results are reported from prolonged administration of large doses of streptomycin, but these result in toxic effects disproportionate to the benefits. It seems more promising for local application to the leprous ulcerations (G. H. Faget and Erickson, 1947).

The *streptomycin unit* represents a much smaller antibacterial potency than the penicillin unit; for instance, 1/12 with one organism (I. G. Anderson and Jewell, 1945).

In vitro, the potency of streptomycin is markedly decreased by salts, and especially by human serum (25 to 50 per cent; S. Berkman *et al.*, 1947).

Absorption of streptomycin occurs rapidly from hypodermic or intramuscular injection, but little is absorbed from oral administration. With 420,000 units by mouth it could not be detected in the plasma, and very little in the urine (B. E. Graham *et al.*, 1946), though more in the feces (H. A. Zintel *et al.*, 1945). It is not inactivated by the gastric juice (Anderson and Jewell, 1945), nor in the intestines.

The *blood concentration* is maintained somewhat better than with penicillin. With 3,000,000 units daily by continuous intravenous injection, the blood concentration ranges between 20 and 60 units per cubic centimeter. After a single intravenous injection of 600,000 units it averages 33 units per cubic centimeter in fifteen minutes, 5 units after six hours. With the same dose hypodermically, the maximal blood level is not attained for two or three hours (Zintel *et al.*, 1945). The curve for intramuscular injection does not differ significantly from the intravenous, except during the first minutes (Anderson and Jewell, 1945). Maximum levels obtain for one to three hours, then decline gradually over ten to twelve hours (C. S. Keefer, Blake *et al.*, 1946).

The streptomycin is *distributed* through most body fluids; the concentration in cerebrospinal fluid is low (Zintel *et al.*, 1945). It passes into the fetus, but in somewhat lower concentration (review, Keefer, Blake *et al.*, 1946).

Streptomycin is *excreted* by the urine, somewhat more slowly than penicillin. From 46 to 87 per cent may be recovered within forty-eight hours (Anderson and Jewell, 1945. In dogs, a fourth to two-thirds of the dosage is excreted by urine; Graham *et al.*, 1946). Its urinary concentration is considerably higher than in the blood. The urine of patients receiving 2 million units daily contains up to 1330 units per cubic centimeter (H. F. Helmholz, 1945). Some is excreted by the bile (Keefer *et al.*, 1946).

Untoward reactions are not infrequent, but are rarely serious. They increase with the dosage. Minor effects consist in skin rashes, malaise, muscle soreness, drug fever and eosinophilia. Some lots produced histamine-like reactions, sometimes severe, with fall of blood pressure and syncope. These are due to impurities and are now rare. A neurotoxic action on the eighth nerve occurs in up to 10 per cent of patients receiving large doses over long periods, with symptoms of vertigo, tinnitus, ataxia and diminished acuity of hearing. It improves after discontinuing the administration, but the recovery is slow and may be incomplete. There is no evidence of renal or hepatic insufficiency (Anderson and Jewell, 1945; Hettig and Adcock, 1946; Molitov, 1946).

In animals, the LD$_{(50)}$ of streptomycin is about 750 mg. per Kg. Monkeys show no toxic effects when 25 mg. per Kg. were injected daily for sixty-six days. Susceptible species develop fatty metamorphosis of the parenchymal cells of the liver, and to a less extent of the renal tubular epithelium. The lesions disappear rapidly after the drug is withdrawn. They are produced by the crystalline as well as by crude preparations (Hettig and Adcock; Molitor, Graessle *et al.*, 1946).

Streptothricin has a delayed toxic reaction on animals, also producing the fatty liver and renal changes (Muskett and Martland, 1946).

Administration of streptomycin must be parenteral; oral administration is useless. Intramuscular injections, repeated every three to four hours, are preferred for systemic effects. In meningitis this is supplemented by intrathecal injection; in empyema, by intraperitoneal; in peritonitis it is sometimes injected intraperitoneally (C. S. Keefer, Blake *et al.*, 1946). Large doses when applied directly to the cerebral cortex produce convulsions (H. C. Johnson, Walker *et al.*, 1946).

For intramuscular injection, streptomycin is dissolved in physiological saline solution, at the rate of 100 to 200 mg. per cubic centimeter. Hypodermic injections must be more dilute. For intravenous drip, it is used at the rate of 1 to 2 Gm. per liter of saline, injected at the rate of about 25 drops per minute. For intrathecal injection, 10 to 20 mg. per cubic centimeter of saline solution.

The dosage for severe fulminating infection is 2 to 4 Gm. daily, in divided doses; for less severe, 1 to 2 Gm. may suffice. The injections should be continued for forty-eight to seventy-two hours after the temperature is normal and all signs of infection have disappeared. It is important to give the full dosage at the start, since fastness may develop rapidly (M. Finland, Murray *et al.*, 1946).

Streptomycin resistance can be produced in gonococci and meningococci by progressive cultivation in media with increasing concentrations of the drug. The resistant meningococci remain fully virulent and produce fatal infection in mice, notwithstanding streptomycin treatment. There is no crossed resistance to penicillin, and vice versa (C. P. Miller and Bohnhoff, 1946, 1947; C. A. Chandler and Schoenbach, 1947).

***Streptomycin,** N.N.R., is the purified antibiotic substance produced by certain strains of Streptomyces griseus when grown on suitable media. It may be prepared as the chloride, sulfate and other salts. It is marketed in airtight ampuls, generally of 1 Gm. It is stable when stored below 15° C. Solutions are less stable and should be freshly prepared for parenteral injections.

OTHER ANTIBIOTIC AGENTS

Tyrothricin is an extract from a soil bacterium, Bacillus brevis, first isolated by Dubos, 1939, which is bacteriostatic and bacteriolytic for several gram-positive organisms. It contains at least two active constituents, *gramicidin* and the much less potent *tyrocidin*. Serum inhibits the latter, but not gramicidin. The bacteriostatic action appears to involve inhibition of the metabolic enzymes of the susceptible bacteria. It is standardized by its protection of mice against intraperitoneally injected pneumococci.

Tyrothricin is used *only locally*, in superficial indolent ulcers, mastoiditis, empyema and some wound infections, and cautiously in body cavities. It is ineffective systemically (H. J. Robinson and Graessle, 1942), and *dangerous by vein*. Its clinical use is in the experimental stage.

Tyrothricin is marketed as a concentrate or as an alcoholic solution, and diluted with isotonic saline so that the solution contains 500 micrograms per cubic centimeter.

Gramicidin S, a bactericidal polypeptide prepared from soil bacteria by Russian investigators, differs chemically from gramicidin Dubos and from tyrocidin. It is reported as a wound antiseptic effective against both gram-positive and negative organisms (Gause and Brazhnikova, 1944).

Clavacin (*Patulin*), a substance which has been isolated in crystalline form, is found in Aspergillus clavatus (Waksman *et al.*, 1942), in Penicillium clavatum and in P. patulum. It is bactericidal in fairly high dilutions to both gram-positive and negative bacteria, and arrests the development of various pathogenic fungi, in 0.5 per cent dilution (J. A. Herrick, 1945). It is highly toxic on intravenous or intramuscular injection, but not with oral or local administration. It is active against gram-negative and positive bacteria and fungi (Katzman *et al.*, 1944). Nasal instillation was reported effective against colds, but thorough and extensive clinical trials by the Medical Research Council of Great Britain failed to demonstrate any value (J.A.M.A., *126*:510).

Bacitracin is an antibiotic substance in the filtrate of B. subtilis cultures, effective against a wide range of bacteria. It is neutral, thermostable, nontoxic, on intravenous injection, nonirritating to the conjunctiva, nonhemolytic, resistant to proteolytic enzymes. It is a polypeptide (B. A. Johnson *et al.*, 1945).

Most of the aerobic and anaerobic cocci of surgical infections, but none of the gram-negative aerobic bacilli, are susceptible to bacitracin as well as to penicillin. Good clinical results are reported from the local application of bacitracin in surgical infections, especially those by staphylococci and nonhemolytic streptococci which resist penicillin and sulfonamides (H. L. Meleney and Johnson, 1947).

Subtilin, isolated from some strains of B. subtilis, is effective experimentally against some infectious diseases caused by gram-positive bacteria. It is relatively nontoxic to vertebrate tissues (A. J. Salle, 1947).

Nocardia, a mold, has yielded a substance that appears to inhibit tuberculosis (E. W. Emmart, 1947).

Tomatin, an antibiotic substance isolated from tomato leaves, inhibits several fungi (T. D. Fontaine *et al.*, 1947).

ANTISEPTIC BENZENE DERIVATIVES

These differ from the antipyretic derivatives by greater toxicity. On local contact they coagulate proteins, thus determining the death of cells, resulting in irritation and inflammatory changes and in antiseptic effects. After absorption they produce some excitement and more pronounced depression of the central nervous system. Many alter the blood pigment to methemoglobin. Their effects are similar in principle, but differ in important details. The high toxicity is due to side chains, such as the hydroxyl and carboxyl groups, by which they can react with protoplasm.

Historical.—In the form of the natural mixtures, the antiseptic properties of this group have been long known empirically, as in the smoking of meat. One of the methods of embalming practiced by the Egyptians utilized largely balsams and products rich in essential oils—the latter closely related to the aromatic series. The isolated substances belong to the achievements of the nineteenth century. Creosote was first made in 1832, phenol in 1834; but almost thirty years elapsed before they were employed to combat infection in surgery. Various antiseptics had indeed been used for centuries in wound treatment, not with the idea of killing living infective agents, but of preventing the putrefaction of the blood and tissues which was supposed to produce injurious matter, the "materia peccans."

The **field of antiseptics** has become considerably restricted since they were introduced by Lister. They can be highly effective outside the body, but they rarely penetrate sufficiently to kill bacteria in living tissues; when they do penetrate, they are generally more effective in killing the tissue cells than the bacteria. They do not really disinfect the tissues, but may kill and embalm the bacteria on the surface. This has a more limited value.

Toxicity and Resistance.—By highly impenetrable cell walls, and by the formation of very resistant spores, bacteria are able to survive conditions which would kill other cells. Under these adverse conditions the microorganisms are unable to grow and multiply; but by passing into a dormant state, particularly by spore formation, they are able to preserve their vitality for a considerable time, and to recover their power of growth as soon as the conditions become more favorable. Substances which merely suspend the vitality of bacteria are *bacteriostatics;* those which kill them outright are *bactericides. Deodorants* obscure or destroy the odorous bacterial products, but have little action on the bacteria themselves.

The Influence of Proteins and Other Organic Matter.—Many substances which are strongly germicidal when acting on the bacteria alone are much weakened by entering into chemic reactions with the medium. Potassium permanganate is *destroyed* by all organic matter; mercuric chloride is *precipitated* by proteins; silver nitrate by chlorides, and so on. These insoluble combinations are no longer germicidal. They *hinder the penetration* of the antiseptic, a condition of considerable surgical importance. The antiseptics of the aromatic series are relatively little affected. From the standpoint of antiseptic efficiency and penetration, the phenols stand high, but they are impeded by serum, even when there is no precipitation (Bechhold and Ehrlich, 1906). The flavine dyes are effective in serum.

The Disinfecting Power of the Commonly Used Antiseptics.—On account of the different resistance of different bacteria, and the ease with which the antiseptic action is modified by circumstances, the results of experiments directed to comparing the different antiseptics cannot be generalized. Tables of antiseptic values are therefore unsatisfactory. Some antiseptics act fairly uniformly on all bacteria; others, especially the dyes, show a high degree of specificity. The relative susceptibility of bacteria and cells was investigated on tissue cultures by R. A. Lambert, 1916.

Penetration of Antiseptics.—The limitations are illustrated by Hirschfelder and Novak, 1938, who injected a small quantity of a staphylococcus culture under the skin of guinea pigs. The bacteria were not killed by any antiseptic applied to the intact skin, or to forty-eight hour granulation tissue. On scarified skin, continuous packs with antiseptics were fairly successful. The penetration increases when the vitality of the cell is lowered, more or less proportional to the injury, as judged, for instance, by the slowing of ciliary motion (V. A. Badetcher, 1933). Dead cells are most permeable and may indeed concentrate antiseptics by adsorption. *Vital stains* penetrate to some extent into living cells, and stain the vacuoles and other inclosures. The cytoplasm proper is generally not stained until it is dead (Dufrenoy, 1933).

Influence of Structure on Action.—Benzene, C_6H_6, has a low toxicity, because it does not readily react with protoplasm. This capacity is given to it by replacing part of the H atoms by other groups, especially by OH (forming phenols) or by CO_2H (forming acids); or by both. The *OH radical* is the most active, the antiseptic and toxic actions increasing with the *number of OH groups* (*i. e.*, progressively from phenol, C_6H_5OH, to resorcin, $C_6H_4(OH)_2$, and pyrogallol, $C_6H_3(OH)_3$), but it is also influenced by the position. The para compounds are the most effective, meta least, ortho intermediate. This holds for all substitute groups. The introduction of the *CO_2H group alone* (*i. e.*, benzoic acid, $C_6H_5.CO_2H$) does not render the substance very active. The antiseptic quality may also be brought out by *other acidyl groups* ($COCH_3$, and the like), the activity being proportional to the size of the introduced radical. NO_2 develops the antiseptic action, but adds its own toxicity to that of the phenols. The substitution of an H of the C_6H_5 in phenol by *alkyls* (*cresols*, $C_6H_4{<}^{OH}_{CH_3}$) leads to an increase of the antiseptic power, and diminishes at the same time the toxicity to tissues. The *substitution of halogens* increases the antiseptic action, according to the number of atoms. The toxicity is diminished by the lower, increased by the higher numbers (Bechhold and Ehrlich, 1906). The violence of the action may be moderated by using esters ("Nencki's salol principle") which develop their action when decomposed into their phenol. Combinations which are so firm as to prevent this liberation (*e. g.*, the phenolsulfonates) are neither antiseptic nor toxic: it is by the formation of such compounds that the organism protects itself against these poisons. The antiseptic and local actions of the salicylates or other *salts* are also much less than those of the corresponding acids.

Fate of the Benzene Derivatives in the Body.—The six-carbon ring is relatively resistant to decomposition, and for the most part passes through the body unbroken, although up to one-half may be burned. The hydrogen atoms and side chains undergo more or less oxidation, resulting in new hydroxyl and carboxyl groups (phenols and acids). These enter conjugations before being excreted by the urine; the phenols form esters, chiefly with sulfuric acid (Baumann and Herter, 1876; O. Neubauer, 1901), and to a less extent with glycuronic acid. The aromatic acids combine with glycocoll to form hippuric acid, and so forth.

Extent of Destruction.—Of the phenol normally absorbed from the intestine, about half is oxidized and half conjugated. Paracresol is oxidized more rapidly than phenol (Pelkan and Whipple, 1922). The exclusion of the bile from the intestines, by increasing intestinal putrefaction, increases phenol elimination (Dublin, 1917). The normal phenol excretion (largely paracresol) tends to vary directly with the protein intake (Folin and Denis, 1915).

Distribution.—When phenol is administered orally, the level of the free and especially of the paired phenols of the blood rises, reaching a maximum in half an hour and returning slowly to the normal, which is reached in six to twelve hours. The conjugation is completed in an hour. The tissues take up a higher percentage of phenol than the blood. The urinary excretion parallels the concentration in the blood. If phenol is injected intravenously (500 mg., dog), a sixth disappears from the blood during the injection, and the normal level is restored in an hour (Pelkan and Whipple, 1922).

Protective Function of Conjugation.—The formation of the esters is generally proportional to the toxicity of the phenols (S. Fraenkel). Since the esters are much less toxic than the phenols they constitute an important protection of the organism against poisoning, especially against the phenols arising in intestinal putrefaction.

Origin of Sulfonate.—This is not derived from sulfates or other inorganic sulfur compounds, for the administration of these does not increase the conjugation. The phenolsulfonates may be formed with a purely carbohydrate diet, so that the sulfur must come from the oxidation of tissue protein, presumably from the cystine; and the quantity can be considerably increased by feeding this amino acid (Shiple and Sherwin, 1923). Considerable phenolsulfonate is produced on incubation of phenol with *slices of liver* (F. Bernheim and Bernheim, 1943). The conjugation is inhibited by 0.0003 M. bisulfate, 0.005 fluoride, 0.002 monoiodoacetate, 0.01 azide, 0.02 oxalate (De Meio and Arnolt, 1945).

Role of the Liver in Conjugation.—The liver takes an important part in the oxidation and conjugation of the phenols (Pelkan and Whipple), although other tissues are probably also concerned. The phenol destruction and conjugation are therefore greater with oral than with intravenous administration, and they are diminished by liver injury; for instance, by chloroform poisoning (Pelkan and Whipple). The sulfo-conjugation has been proposed as a test of hepatic function. Thymol, 0.5 Gm., is normally followed by considerable increase of the ethereal sulfates of the urine. This increase is sometimes absent in hepatic disease, but not always (M. Kahn, 1918). Chloroform and carbon tetrachloride poisoning of rabbits decreases the ratio of organic to inorganic sulfate excretion; phosphorus poisoning does not. Glycuronic acid excretion was not affected by liver injury (Deichmann *et al.*, 1945).

Glycuronic acid corresponds to dextrose, with the end chain (CH_2OH) oxidized to ($COOH$). It is probably an intermediate stage in the oxidation of glucose, for very little can be formed in glycogen-poor animals (Dakin). Glycuronic acid is probably not a normal stage of carbohydrate metabolism; for if it is administered parenterally, it appears almost quantitatively unchanged in the urine (Biberfeld, 1914). The *source* of the glycuronic acid is probably from glycogenic substances rather than from mucin, as had been suggested (Ambrose and Sherwin, 1934). It is never excreted free, but always in combination with aromatic alcohols, phenols, ketones and acids. Haemaelaeinen, 1913, supposed that the alcohols first combine with glucose, and that this glucoside is then oxidized to the glycuronate. Slices of liver in saline phosphate medium produce conjugated glycuronic acid in the presence of phenol, borneol or menthol. This is significantly increased by addition of sodium lactate or pyruvate. It is disturbed in phosphorus-poisoned animals, but apparently not by chloroform poisoning (Bueding and Ladewig, 1939). The glycuronic compounds may be mistaken for sugar, since they reduce copper, although more slowly. The principal *drugs which cause the appearance of glycuronic acid in the urine* are: turpentine, chloroform, chloral, camphor, phenacetin, saccharin, salicylic acid, balsams, morphine.

PHENOL

Phenol, carbolic acid, $C_6H_5.OH$, became widely known as an antiseptic through its introduction by Lister, 1867. Some of its derivatives are superior, at least for special purposes.

Antiseptic Action.—Phenol is a general protoplasmic poison and a fairly active antiseptic, although not nearly so potent as mercuric chloride, or even as the cresols. It precipitates proteins, but the combination is so loose that it readily diffuses further, and therefore penetrates more deeply into the tissues than the metallic antiseptics; and its action is not so much hindered by the presence of organic matter. The *disinfectant power* varies greatly for different micro-organisms; spores are especially resistant. Tubercle bacilli are killed by exposure to 5 per cent for twenty-four hours. It is much more effective for checking bacterial growth; ½ to 1 per cent suffices for this purpose. These are the concentrations used on the body, for here it is not necessary to kill the bacteria if their development is effectively prevented. These solutions do not ordinarily injure the tissues.

Antiseptic Uses.—Five per cent solutions are used for the disinfection of the utensils, instruments, the hands, and so forth. The penetration and therefore the antiseptic efficiency are increased by the addition of salt. "Crude Carbolic Acid," which contains the more active cresols and is cheaper, is preferred for the disinfection of excreta. As antiseptic for wounds and mucous membranes, gargles, lotions or injections, ½ to 1 per cent of phenol is used. A drop of undiluted phenol is useful for disinfecting and cauterizing small wounds, bites, and the like. Injections of phenol have been tried against local inflammations, tuberculous bones and lymph glands, boils, erysipelas (5 per cent to scarified surface), and so on. Lotions are used as parasiticide in scabies, sycosis, pityriasis and against pediculosis capitis. Inhalations have been advocated in fetid bronchitis and pulmonary gangrene, but at best are only deodorant. As intestinal antiseptic, phenol has no value, because of its prompt absorption and marked toxicity.

Phenol Injections in Tetanus.—Baccelli used rather large doses, a 2 to 3 per cent solution injected intravenously or hypodermically along the spine every two or three hours, the *daily* dose starting with 0.2 to 0.5 Gm., and increasing rapidly to 0.8 to 1.5 Gm. of absolute phenol in divided doses, according to severity (J.A.M.A., *53:* 2140, 1909). No bad effects have been reported, and it is said to cause improvement and to decrease the mortality, even in severe cases (Ascoli, 1913). McClintock and Hutchings, 1913, stated that it has only a limited value, as a simple sedative. Joffe, 1914, commended it. Fielder, 1914, obtained negative results in *rabies*.

Pediculosis Capitis.—Whitfield, 1912, advised soaking the scalp in a 2.5 per cent phenol solution for ten minutes and leaving the solution on the hair for an hour.

Actions on Ferments.—Phenol, salicylic acid and other coal tar antiseptics retard *ferment action*. A 5 per cent solution of phenol suffices to weaken materially the action of most ferments.

Solutions of phenol in fatty oils are not antiseptic (Koch, 1886), because its solubility in fats is so much greater than its solubility in protoplasm that it prevents its transference to the bacteria or tissues. "Carbolated Oil" is merely a mild local anesthetic and dermal irritant. Alcohol and glycerin have a similar restraining action. The solubility in petrolatum is small, so that ointments made with this base are more actively antiseptic and irritant.

Local Actions.—Concentrated phenol applied to the skin or mucous membranes produces prickling, burning and pain, then numbness and anesthesia, wrinkling and softening of the epidermis; the color of the skin becomes first white, then red and finally brown. There is no direct corrosion, but a local necrosis. A dry scab forms, which separates without pus. Short applications of weaker solutions determine merely some wrinkling and blanching of the epidermis and the sensory phenomena, but a 5 per cent solution of the acid may cause necrosis, especially when applied continuously to the extremities. This enjoins caution in the use of carbolic dressings. Even dilute solutions should not be covered with dressings that preclude evaporation. Systemic poisoning may result from prolonged application to extensive surfaces. Good solvents of phenol, such as glycerin, alcohol and volatile or fatty oils (but not mineral oils) diminish the degree, but prolong the duration, of the local actions. The analgetic action of phenol solutions (1 per cent) or ointments (2 to 4 per cent, *f. i.*, in cold cream) is used against *itching* and *herpes;* but menthol (1 per cent in alcohol, 1 or 2 per cent in cold cream) is less toxic and more effective.

Undiluted phenol may be used for quick *local anesthesia of the skin*. A scalpel wet with phenol is drawn over the proposed incision, which may be made after a few seconds (Soresi, 1919). A minute drop applied to a *carious tooth* relieves the pain. A small and harmless amount penetrates to the pulp cavity (B. O. A. Thomas, 1941). A 5 per cent watery solution applied to an exposed nerve causes *anesthesia* (Schleich).

The ratio of toxicity of antiseptics to tissue cultures in comparison to antiseptic potency is reported as 0.29 for iodine, 0.64 for azochloramide, 2.7 for phenol, 3.4 for zephiran, 3.9 for merthiolate, 4.1 for saponated cresol (G. H. Paff *et al.*, 1945).

Phenol Camphor.—When camphor and phenol are rubbed together they liquefy. Mixtures of this kind (phenol 30, camphor 60, alcohol 10, known as "Chlumsky's Solution") have been employed on suppurating wounds and abscesses, with the claim that the caustic action is diminished and the analgetic and antiseptic efficiency increased. The latter is doubtful, but the decrease of irritation agrees with the effects of all good phenol solvents. There is no chemic combination (Yvon, 1876; Lemberger, 1906), but F. Müller, Günther and Peiser, 1927, claimed that the mixture used in surgery is a loose molecular compound which is destroyed on contact with water or watery secretions, separating (experimentally) into a 1.3 per cent aqueous phenol solution and finely divided camphor. Chlumsky, 1905 and 1913, recommended phenol camphor in superficial inflammatory conditions, especially erysipelas, painting it on and around the affected area. F. Pohl, 1913, and Schiele, 1914, injected 2 to 5 cc. into diseased joints, without bad effects; 30 to 50 cc. were used for irrigating abscesses. It has been recommended against *athlete's foot* (E. Francis, 1941), but perspiration may render it caustic (H. G. Calvery, 1942).

Absorption.—Phenol is absorbed from all mucous membranes and wounds, and from the intact skin. In the intestinal canal its absorption is at first rapid, but soon becomes almost arrested, apparently by interference with the local circulation (Sollmann, Hanzlik and Pilcher, 1910). It is distributed through all the tissues.

Fate.—A part of the phenol (¼ to ⅔) is completely burned in the body (Tauber, 1878). The remainder is excreted in the urine, largely as ethereal sulfates and glycuronates of phenol, hydroquinone and pyrocatechol. The oxidation products impart the smoky color to the urine.

Normal rabbit tissue contains from 0 to 39 mg. of free phenol per 100 Gm., and 1.15 to 19 mg. of conjugated. Small amounts of *administered phenol* are conjugated and excreted. With doses that exceed this capacity, about half is destroyed by oxidation, chiefly to carbon dioxide and water; the excreted undecomposed phenol, pyrocatechol and hydroquinone are largely conjugated. These hydrolyze on exposure to air, forming substances of *smoky color* (W. B. Deichmann, 1944). Folin and Denis, 1915, found that 30 to 90 per cent of the urinary phenol is not conjugated. With a rise of total phenol, a greater proportion is conjugated, except when bile is excluded from the intestines (Dubin, 1916). A trace of phenols is found in the sweat (Tachau). *Surviving tissue slices* of liver, and kidneys to a less degree, form conjugated glycuronic acids from phenol, menthol, borneol and avertin. The oxidation necessary for this is catalyzed by heavy metals, inhibited by cyanide, iodo-acetic acid, fluoride and hypnotics (Lipschitz and Bueding, 1939).

Central Actions.—Very small doses of phenol produce at first an *analgetic and antipyretic action.* This is so fleeting, and passes so readily into the graver effects, that it cannot be used in therapeutics. It is followed by more pronounced symptoms resembling the "toxic" effects of salicylates. Dangerous doses produce prompt collapse and coma. Frogs and mammals exhibit characteristic muscular tremors, twitchings and convulsions, persisting until the blood pressure falls very low. These are absent, or at most very faint, in man (Husemann, 1871).

Phenol Convulsions.—Salkowski, 1872, showed that these are located in the spinal cord (division of sciatic; decapitation). Morita, 1915, also found that the convulsions occur in rabbits after ablation of the hemispheres. Baglioni, 1900 and 1909, by the methods explained under strychnine, concluded that the convulsions depend on increased excitability of the spinal motor cells. Direct application of dilute phenol solutions to the exposed spinal cord produces anesthesia. The excitability of the *motor cortex* is lowered by its local application (Baglioni and Magnini, 1910), without convulsions (Amantea, 1913). *Muscle and nerve fibers* are paralyzed by local contact with strong solutions, but do not seem to suffer if the drug acts systemically. In *frogs,* phenol produces successively local reflex irritation, short stupor, a medullary cry, then gradually the twitchings and irregular and incoordinated contractions. The reflexes are preserved, but naturally ineffective because of the interference and interruptions of the convulsions (Baglioni; Arloing and Thevenot, 1920).

Circulation.—Intravenous injections of phenol, even with small doses, cause marked fall of blood pressure, usually with rapid recovery until a certain dosage is exceeded. The fall appears to be both cardiac and vasomotor. When phenol is given by stomach, the blood pressure remains low because of the continuous absorption (Sollmann and Brown, 1906).

The *vasomotor center* is usually depressed, probably directly. This may be modified by indirect stimulation through the convulsions or ischemia. The center may therefore be stimulated, or a period of stimulation may precede or follow the depression period (Pilcher and Sollmann, 1915). Phenol causes an increase of *secretions,* especially of saliva, sweat and tears, not yet explained.

Respiration, Temperature and Collapse.—The *respiration* becomes slow and shallow, and finally stops. The *temperature* falls. Since the collapse affects all the medullary centers, and the cardiac muscle as well, it cannot be removed by artificial respiration. The *sensibility to pain* is often *preserved* far into the collapse. The local effects of the phenol play no important part in the production of the collapse (Sollmann and Brown, 1906).

Toxicology.—Suicidal poisoning by "carbolic acid" is common. Accidental poisoning may result when the phenol is applied to the intact skin; its liberal application to open surfaces has frequently led to toxic symptoms. The *fatal dose* by mouth varies between 8.5 and 60 Gm. (Lewin); 0.8 Gm. has been given therapeutically without bad effects. The systemic toxicity is about the same by mouth and hypodermically (Hale, 1913). It depends on the dose; and for the skin, on the area exposed, not on the concentration (Deichmann and Witherup, 1944). The course of carbolic acid poisoning is *rapid.* In almost all fatal cases death ensues inside of twenty-four hours. The *local symptoms* consist in burning of the mouth and throat, nausea and vomiting, abdominal pain. Carbolic burns generally heal promptly, with small tendency to scar formation. The *systemic symptoms* are those of a speedy *collapse,* starting in a few minutes, even when the drug is taken by mouth. It is manifested by faintness and muscular weakness; rarely twitching and convulsions; pulse small, weak and slow; face livid; cold sweat; respiration slow and shallow; unconsciousness; coma; death by stoppage of respiration. The *urine* is scanty and often contains albumin and casts, sometimes hemoglobin or the bile pigments. It has a dark, smoky color, especially on standing, from the oxidation of the hydroquinone, pyrocatechin, and the like, that are formed from phenol. It gives little or no sulfate precipitate with barium chloride. These points are of diagnostic importance. The urine rarely contains traces of uncombined phenol. *Surviving patients* may show vesical and renal irritation, and sometimes prolonged weakness and unstable temperature.

Chronic Phenol Poisoning.—In the days of the Lister spray, chronic phenol poisoning was common among surgeons. It showed the general symptoms of marasmus. Two Gm. of phenol were recovered from the urine of a surgeon who had assisted for two and one-half hours at an operation under a 2 per cent spray (Falkson, 1881) Minor grades may occur from carbolic applications. They often show skin eruptions (Lewin) and renal irritation (kidney changes, Uyeno, 1909). Chronic phenol poisoning sometimes occurs *in industry*. The symptoms consist of digestive disturbances, skin eruptions, nervous disorders with headache, faintness, vertigo and mental changes (H. Zangger, 1928). Dogs tolerate oral administration of 0.4 Gm. twice a week for nine months. Larger doses may produce dyspnea and sudden death (M. Biebl, 1934). Deichmann *et al.*, 1944, found that oral and hypodermic sublethal toxic doses cause pulmonary injury, and later damage to the heart, liver and kidneys. *Inhalation* of 0.1 to 0.2 mg. per liter of air for seven hours daily produces chiefly progressive pulmonary irritation in guinea pigs and rabbits. Rats are relatively resistant.

Phenol-Contaminated Drinking Water.—Heller and Pursell, 1937, reported that the addition of 0.5 to 0.8 per cent of phenol to the drinking water does not interfere with the growth, reproduction or lactation of rats. Nutritional disturbances appear when 1 per cent of phenol is added. The low toxicity is apparently due to conjugation. However, Deichmann and Oesper, 1940, found that 0.2 per cent resulted in retardation of growth and diminished resistance to intercurrent pulmonary infections. Goldfish tolerate 0.0025 per cent (Sollmann).

Treatment of the Local Effects.—These are removed by *promptly* washing with alcohol (or whisky) and applying an oil dressing. Alcohol, fats, glycerin, turpentine and ether act simply by their solvent affinity for phenol, preventing its penetration into the tissues or dissolving it from them (Sollmann, 1906). Soap with plenty of water is recommended by Deichmann and Witherup, 1944.

Treatment of Internal Poisoning.—The best success is obtained by *lavage* of the stomach with warm water, or first with 10 per cent alcohol, taking care that the fluid does not enter the trachea. The washing must be continued till the phenol odor disappears. It should be attempted even if an hour or more has elapsed since the poison was swallowed (D'Hotel, 1907), because a large part of the phenol remains for a long time unabsorbed in the stomach (Sollmann, Hanzlik and Pilcher, 1910). Olive or cottonseed oil are distinctly beneficial; as large a quantity as possible should be swallowed. This checks the local action and the absorption and also facilitates the passing of the stomach tube. There should be further extensive gastric lavage with oil, finally leaving some clean oil in the stomach (L. Goodman and Geiger, 1935). Chemic antidotes, alcohol and sulfates are practically useless. Intravenous saline infusions have some value against the circulatory depression; and heat has some against the collapse.

Lime forms an insoluble compound and is fairly effective (Husemann and Ummethun, 1870). Syrup of lime may be given freely; lime water is too weak. *Permanganate* destroys phenol, but the ordinary doses are not efficient. Tincture of *iodine* was suggested by Maberly, 1909. Schoville, 1913, claimed that charcoal is useful. *Alcohol* was formerly considered a chemic antidote, supposedly effective even when left in the stomach. Both the clinical and experimental evidence disprove this view (Clarke and Brown, 1906). Its solvent action is useless if it is left in the stomach to be absorbed. It does not diminish either the severity or the duration of the symptoms (Dunn and Perley, 1931). *Sulfates* have been given with the object of forming the nontoxic phenolsulfonates. This combination does not occur in the alimentary canal, and the sulfates are slowly absorbed, so that oral administration is useless except in chronic poisoning. The combination is so slow that it is practically not available in acute poisoning, even if the sulfate is injected intravenously (Brown and Sollmann, 1906).

Preparations.—***Phenol**, U.S.P. (Hydroxybenzene, Carbolic Acid), C_6H_5OH, occurs as needle-shaped crystals, colorless, but acquiring a reddish tinge by oxidation of traces of the phenol to quinone and other derivatives (Gibbs, 1909). Characteristic odor and sweetish caustic taste. Melts at about 38° C.; sol. in water (1:15); miscible in all proportions with alcohol, glycerin and fats; dissolved by alkalis. The solubility in water diminishes with the temperature, and can be increased by the addition of alcohol or glycerin. Phenol is sometimes faintly acid to litmus, but this is due to impurities (E. Schmidt, 1911). It is not a true acid, either chemically or physiologically. It is *incompatible* with iron and collodion. Dose, 0.06 to 0.2 Gm., 1 to 3 grains, diluted. *Liquefied Phenol*, U.S.P. (Phenol Liquefactum), contains 10 per cent water. It is more convenient for dispensing. When diluted with an equal volume of glycerin, the mixture is miscible with water. Dose, 0.06 cc., 1 minim. *Phenol Ointment*, U.S.P., contains 2 per cent each of phenol and of glycerin in White Ointment. *Carbolized Oil* usually contains 5 per cent. *Compound Solution of Sodium Borate* (Dobell's Solution), contains 0.3 per cent of phenol, and 1.5 per cent each of sodium bicarbonate and borate.

Phemerol Chloride, N.N.R., is a complex phenyl and ammonium compound, sold as a 1:1000 aqueous solution and 1:500 Tincture. It is used as antiseptic and germicide, undiluted except in the eye and nose; for these it should be diluted with four volumes of water.

Phenolsulfonates or Sulfocarbolates are less toxic and irritant, but also much less antiseptic than phenol. They have little value.

CRESOLS

The introduction of alkyl groups into phenol greatly increases the germicidal efficiency. The most important of these derivatives are the cresols, $C_6H_4OH.CH_3$, obtained from "crude carbolic acid." Attention was directed to their properties by Fraenkel, 1889. The three isomers, ortho-, para- and meta-cresol, differ somewhat quantitatively, the meta being the most antiseptic and least toxic, and para the most toxic; but they are all contained in variable proportions in the commercial products usually employed. The *germicidal power* averages three or more times that of phenol; preparations containing higher homologues (N.N.R.) may be fifteen times more potent than phenol. The *toxicity* of the cresols is of the same order of magnitude as phenol (Tollens, 1905; Hale, 1913; toxicity and fate, Jonescu, 1906), and they produce almost identical effects and lesions with relatively less convulsions and more collapse (Deichmann and Witherup, 1944). They are excreted for the most part conjugated, but otherwise unchanged. The *treatment* of poisoning would be similar. In practice, they are less toxic than phenol, because they are used *more diluted*, but they are far from being "nonpoisonous." Another advantage over phenol is their lower cost. Their *disadvantages* are the disagreeable odor, which depends mainly on impurities; their limited solubility in water; and their variable composition and activity. Organic matter slows their action rather more than with phenol. Acid and hard and salty water hinder them by precipitating the soap by which they are usually dissolved (Hamilton, 1914).

The *toxicity of ortho-n-alkyl phenols* by oral administration to rats decreases with the length of the alkyl chain. This holds true also for alkyl-meta-cresols and alkyl resorcinols (H. W. Brown and Lamson, 1935).

Solutions and Application.—The cresols may be rendered soluble by the addition of soap, as in the official Compound Cresol Solution, and in other ways. The soap mixtures partake of the slippery nature of soap and are therefore less useful in operating, but they are well adapted to cleansing the hands (brushing for two or three minutes with ½ to 1 per cent solution) and for other purposes. A dusting powder containing 3 per cent of tricresol has been recommended for pediculosis (Herxheimer and Nathan, 1915).

Serum Preservation.—Tricresol, 0.25 per cent, is often added to secure the preservation of serums. This is harmless with the usual hypodermic injections, but may be a factor in the collapse that sometimes follows *intraspinal injection*, especially of the antimeningitis serum (Voegtlin, 1914; Livingston, 1920). The experiments of Auer, 1914, on monkeys render it improbable that the ordinary concentrations do any harm. Clinically, it has marked advantages, being more bactericidal than chloroform, and markedly analgetic (J. B. Neal and Abramson, 1917).

With *antipneumococcic serum*, a further danger might arise from the intravenous injection of relatively large doses. However, Voegtlin, 1918, found no danger of toxicity if the concentration does not exceed 0.5 per cent and if the injections are made slowly.

Phenol Coefficient.—The variability of the cresols may be discounted by the determination of the "phenol coefficient," *i. e.*, the ratio of the germicidal power of the disinfectant to the germicidal power of phenol, both being tested under identical conditions, as described in U. S. Public Health Reports, 1921, page 1559. A disinfectant three times as potent as phenol would have the coefficient 3, and so on. The phenol coefficient is valuable only for the disinfectants related to phenol; not for metals, iodine, chlorine, and so forth. Criteria for the evaluation of skin disinfectants were set down by the Council on Pharmacy and Chemistry, 1943, J.A.M.A., *121*:593.

Benzene Derivatives on Insects.—W. Moore, 1917, tested the vapors of a series on house flies. He found that all the benzene derivatives tested had a higher molecular toxicity than carbon disulfide; the physical characters are more important than the chemical composition.

PREPARATIONS.—*Cresol*, U.S.P. (Tricresol, Cresylic Acid), $C_6H_4CH_3OH$, is a mixture of the three isomeric cresols obtained from coal tar. Colorless, yellowish or pinkish refractive liquid, of phenol-like odor, darkening on exposure to air. Sol. in water (1:50), usually forming a cloudy solution; miscible in all proportions with alcohol, ether or glycerin, and dissolving in alkalis. Dose, 0.06 cc., 1 minim, diluted. The following concentrations are employed *for local use: in surgery*, ¼ to 1 per cent; gargles or cystitis, ¼ per cent; cuspidors (tubercle bacilli) or stools, 1 to 1½ per cent; for sponging rooms or soaking clothes, ½ to 1 per cent. To make a 1 per cent solution, add 2 teaspoonfuls to a quart of water. Cresol is generally used in the form of: *Compound Solution of Cresol*, U.S.P., contains 50 per cent of cresol dissolved with a potash-vegetable oil soap. It has a phenol coefficient of about 3, and serves all the uses of the proprietary solutions, with the advantage that it is not advertised under exaggerated and dangerous claims, such as being "nonpoisonous."

Metacresyl acetate is very little soluble in water, and therefore less toxic (Greenwald, 1911). It was tried as a mild antiseptic for mucous membranes.

Commercial Cresol Preparations.—These contain varying amounts of cresol. They may be grouped according to the dissolving agent as (1) *Emulsions* with resin soap or petroleum oils; and (2) *Solutions* with potash soaps (*lysol*) or with sulfo-acids.

Phenoloid Disinfectants.—Cresol mixtures containing the higher homologues are described in N.N.R.

Diphenyl derivatives have been studied for toxicity on animals by Deichmann, Kitzmiller *et al.*, 1947.

TRI-ORTHO CRESYL PHOSPHATE

This produces a peculiar multiple neuritis, which was discovered in the United States early in 1930 as a result of drinking fluid extract of ginger ("Jake") which had been adulterated with this compound (M. I. Smith *et al.*, 1930). It also occurred abroad by similar adulteration of "apiol" (parsley extract). The neuritis involves chiefly the legs and distal muscles. It develops after a latent period of several weeks, even if the drug is administered by vein. The lesions, which are usually permanent, consist mainly in degeneration of the myelin sheath of the peripheral nerve and anterior columns of the spinal cord, and of the pyramidal cells.

Clinical Phenomena.—The characteristic symptoms, bilateral foot drop and wrist drop with loss of Achilles reflex and plantar response, but only occasionally of the patellar reflex, develop in from one day to three weeks (usually four to ten days) after the extract has been taken. The paralysis is preceded by soreness in the affected muscles. In some cases, transient gastro-intestinal disturbance occurs soon after the taking of the extract. The paralysis is always more marked in the feet and legs than in the hands and forearms. There is no sensory disturbance and no involvement of the cranial nerves (C. R. Bennet, 1930; S. Harris, 1930; H. H. Merritt and Moore, 1930; B. Burley, 1930). The autopsy findings are chiefly those of peripheral neuritis (R. H. Goodale and Humphreys, 1931). M. L. Weber, 1937, who followed up thirty-five cases that had been poisoned six years previously, found little restoration of motor function. The disability remained greatest in the legs. Sensation was little impaired, even in severe cases.

Experimental Studies.—M. I. Smith *et al.*, 1930, found that calves and chickens reacted to the suspected extract similarly to humans, and that tri-ortho cresyl phosphate produced the same phenomena. Dogs and monkeys were apparently immune to large doses by oral administration, but developed the characteristic symptoms after intramuscular or subcutaneous injection. Oral administration to rabbits resulted in the phenomena of systemic poisoning by phenol or cresol. These variations in the action on different animals are believed to be due partly to differences in the absorbability from the digestive tract. Typical phenomena are produced by the hypodermic administration of pure tri-ortho cresyl phosphate to cats. The effects are cumulative. The latent period shortens inversely to the dose, the degree of paralysis increases with the dose. Large doses cause rapidly fatal flaccid paralysis (J. G. Kidd and Langworthy, 1933).

Neuropathology.—The lesions are confined chiefly to the myelin sheath of the ventral roots of the spinal cord and to the motor cells of the anterior horn. With longer survival, they may involve also the cells of the dorsal ganglia and the fibers of the dorsal roots (R. D. Lillie and Smith, 1932; Kidd and Langworthy, 1933).

Ortho tricresyl phosphate (but not the meta and para compounds) inhibits *serum choline esterase in vivo* and *in vitro;* this may be the basis of the neurotoxic action. Triorthochlorphenylphosphate also produces this effect (H. Bloch, 1943).

Related Compounds.—Ortho cresol and tricresol are devoid of the neurotoxic action of the phosphate esters. *Mono-ortho cresyl phosphate* also produces only the ordinary phenol actions; *diortho cresyl phosphate* does not produce even these. Both are hydrolyzed fairly rapidly by phosphatases (M. I. Smith, 1934). *Tri-para-cresyl phosphate* is but slightly neurotoxic. Gross and Grosse attribute this to poor absorption. *Triphenyl phosphate* is more extensively neurotoxic than the tri-ortho cresyl phosphate (R. D. Lillie and Smith, 1932). The *phosphite esters* act essentially like the phosphate, but with more rapid and wider extension, even to the bulbar, cerebellar and mesencephalic centers (M. I. Smith, Lillie *et al.*, 1933).

Trimethyl phosphate also has somewhat similar neurotoxic actions (Deichmann and Witherup, 1946).

Hexaethyl tetraphosphate, "HTP," used as insecticide, has a strong inhibitory effect on mammalian and insect choline esterase, *in vitro* and *in vivo*, which accounts for some of its physiologic effects (K. P. DuBois and Mangun, 1947). Great care must be observed in spraying with hexaethyl tetraphosphate, as it is highly toxic to mammals, and is readily absorbed through the skin; 1 mg. per Kg. may produce poisoning, and 5 mg. per Kg. are fatal to some species. It acts chiefly by destroying cholinesterase. The symptoms in man begin with dyspnea and a feeling of tightness in the chest, which should serve as a warning. Severe poisoning in animals produces gastrointestinal symptoms, serious diarrhea, great muscular prostration and apathy (Interdepartmental Committee on Pest Control, April 3, 1947).

POLYATOMIC PHENOLS

The introduction of further OH groups tends to raise the antiseptic, but also the irritant and toxic effects of phenol. The modifications depend largely on the position of the groups: of the three isomers with the two OH groups, *Resorcin*, 1:3, is perhaps somewhat more antiseptic than phenol, and rather less toxic and irritant. *Hydroquinone*, 1:4, is more toxic; and *Pyrocatechin*, 1:2, is much more so. They act as reducing agents, especially in alkaline solutions. Pyrocatechin is not used in medicine. Hydroquinone is not used directly, but is formed from arbutin, contained in Uva ursi. *Pyrogallol*, containing three OH groups, is highly toxic, while its isomer, *phloroglucin*, is practically inactive.

RESORCINOL

Resorcin coagulates albumin. Strong solutions irritate, soften and slowly cauterize the skin; weak solutions are merely antiseptic. It is employed externally in skin diseases, and internally in gastric fermentation and in diarrhea. After absorption, it produces the same effects as phenol, but with more prominent convulsion, occurring even in man; 8 Gm. have caused severe poisoning, but with recovery (Murrel, 1881). Smaller doses are antipyretic, but the action is too short to be useful. They produce "toxic" effects resembling those of salicylates. The fate and excretion are similar to those of phenol.

PREPARATIONS.—***Resorcinol** (Resorcin), U.S.P., $C_6H_4(OH)_2$, 1:3. Colorless, needle-shaped crystals, of peculiar faint odor, and sweetish, then bitter taste

Acquires pinkish tint on exposure to light and air. Very sol. in water (1:1) or alc., freely sol. in glyc. or eth. Dose, 0.06 to 0.3 Gm., 1 to 5 grains; maximum, 1 Gm., 15 grains. On the *skin*, 1 to 50 per cent ointment or 10 to 20 per cent solution in glycerin; 1 to 10 per cent is used as antiseptic and keratoplastic in chromic eczema; 20 per cent is keratolytic. For urethral or vesical irrigation, ½ to 2 per cent. In alopecia, 1 to 2 per cent; however, resorcin discolors light or red hair to a greenish tinge; it does not appreciably alter the color of black hair (H. N. Cole). Resorcin stains may be removed from the skin by citric acid (Mankiewicz, 1916). *Resorcinol Monoacetate*, N.N.R., C_6H_4. (OH) ($OOCCH_3$), tends to liberate resorcinol and has a similar but milder and more persistent action. It does not discolor the hair. It is applied as 5 to 20 per cent ointment or 3 to 5 per cent lotion.

HEXYLRESORCINOL

The introduction of an alkyl radical into resorcinol (analogous to the cresols) increases the germicidal activity and decreases the toxicity. V. Leonard, 1924, introduced hexyl resorcinol, $C_6H_3(OH)_2.(CH_2)_5CH_3$, as an internal antiseptic for the urinary tract, but its action is uncertain (E. Davis and Sharpe, 1932), and it is liable to produce considerable gastro-intestinal disturbance. It is an effective anthelmintic against ascaris and hookworm (P. D. Lamson and associates, 1930, 1931, 1932). It is also advertised as local antiseptic. Its phenol coefficient is high (45), but it has no special advantage, is somewhat irritant and occasionally causes severe local allergic reactions, even with 1:1000 solution (C. W. Walter, 1935).

As anthelmintic, hexylresorcinol is a preferred agent against ascaris and intestinal flukes, and a second choice against hookworm. The crystalline hexylresorcinol in friable capsules of 0.2 Gm. is administered, fasting, as a single dose—5 capsules above twelve years, 2 capsules below six years—followed by water, but no food is taken for the following four hours, as food combines with the drug and renders it inactive. Water may be taken freely and a purgative should be given after twenty-four hours. This treatment usually kills the parasites outright, but repeated treatment may be necessary. It is difficult to administer because of the gastro-intestinal irritation it produces. This is much less with higher alkyl phenols, for instance, heptylphenol and hexylmetacresol, but their clinical efficiency is also much less (Lamson, Mallory and Brown, 1935). The systemic toxicity of hexylresorcinol is negligible, as only a third of the drug is absorbed. *Heptylresorcinol* is less absorbed, about 96 per cent being recovered from the feces (Robbins, 1931).

As urinary antiseptic, hexylresorcinol is administered in gelatin capsules containing 0.15 Gm. in oily solution, to minimize gastro-intestinal irritation. One to 5 capsules are administered daily. There is often decided catharsis, but this usually subsides after a few days, even if the administration is continued. Hexylresorcinol is not suited for hypodermic administration since it would produce local necrosis. The clinical results in some types of urinary cystitis and pyelitis are quite good, but not uniformly so, and B. coli infections are notably resistant. Large doses of sodium bicarbonate diminish its activity, but this is not affected by the natural range of urinary reaction (Leonard and Wood, 1925). There is no evidence of irritation of the urinary tract even with large doses. Rabbits have received 0.5 Gm. daily for six weeks, without toxic symptoms.

Hexylresorcinol, U.S.P., "*caprokol*," is sparingly soluble in water (1:2000), freely in organic solvents. Average dose as anthelmintic, 1 Gm.

Dihydranol (dihydroxyphenyl heptane) seems curative against the natural Balantidium coli infection of guinea pigs, but the effective dose is too close to the toxic (N. A. David and Leake, 1930).

HYDROQUINONE

This compound, paradihydroxybenzene, $C_6H_4(OH)_2$, occurs among the end products of the oxidation of many benzene derivatives, and as it is actively leukopenic, Kracke and Parker suggested that it may be chiefly responsible for *granulocytic neutropenia;* but the evidence is not convincing. Hydroquinone is formed in the cleavage of *arbutin*, a crystalline glucoside which occurs in *Uva ursi*, a plant formerly used as diuretic, acting perhaps by renal irritation. Hydroquinone is employed in photography as a reducing agent. It is a potent bacteriostatic. In *industrial poisoning by hydroquinone*, Velhagen, 1931, observed a peculiar brown coloration of all the corneal layers in the area of the palpebral fissure. He assumed the penetration of crystal dust and its oxidation to paraquinone. Feeding of hydroquinone to black cats was reported to turn their fur gray (quoted from L. Schwartz, 1939). The addition of a small quantity of hydroquinone to *fats* materially delays the onset of rancidity, acting as an "*antioxidant*"; but it remains to be shown that its continued consumption in food is safe. Its employment as a "stabilizing" agent for preparations containing vitamin A is not countenanced (J.A.M.A., 1937, *109:*1454).

Uva Ursi.—This plant has been used for its diuretic and antiseptic effects in vesical catarrh. It contains arbutin, tannic acid and other constituents. *Arbutin* is a crystalline glycoside, yielding glucose and hydroquinone on decomposition. It is decomposed completely in the body (Lewin, 1883; Grisson, 1888); with large doses the hydroquinone appears in the urine (Bass, 1912) and is supposed to be the active agent. Lewin and others found it beneficial in cystitis, and so forth; Paschkis and Feibes, 1884, doubted its efficiency; Bass found no action on healthy men, even with 20 Gm. The usual dose is 1 Gm., three to six times daily.

Quinone, $C_6H_4O_2$, was studied for toxicity by Labes

1929. The *naphthoquinones* (see Index) are discussed in connection with prothrombin formation and vitamin K.

Pyrocatechol.—The systemic toxicity for oral administration to cats and rats was investigated by Dietering, 1938: 50 mg. per Kg. of body weight produces convulsions followed by paralysis, with death in forty-eight hours, by respiratory and circulatory failure. Daily administration of 30 mg. per Kg. results in anemia, icterus, damage to the renal parenchyma, and death in a few weeks. Each dose causes marked hyperglycemia.

PYROGALLOL

The powerful reducing action overshadows the phenol effects. *Locally,* it is a mild caustic for wounds and mucous membranes; it produces but slight irritation of the intact skin, passing into erythemas on continued use. *Absorbed* into the blood, it forms methemoglobin, disrupts the corpuscles and leads to intense acute nephritis. Concentrated solutions acting on blood *in vitro* (not in the body) produce a peculiar insoluble substance, hemogallol. Fatal poisoning may occur even when the drug is applied to the intact skin; and may set in suddenly after it has been used for some time without effects. The *symptoms* consist in diarrhea, and vomiting, chills, prostration, feeble pulse; nephritis with scant dark urine containing blood or hemoglobin derivatives (Neisser, 1881); sometimes icterus and glycosuria. The rapid cases show cyanosis, dyspnea, convulsions and collapse. The *treatment* would be symptomatic. Pyrogallol increases the inhibitory response of the heart of cats and rabbits to stimulation of the divided vagus (Danilewsky and Wjalkowa, 1931).

Pyrogallol (Pyrogallic Acid), $C_6H_3(OH)_3$, is freely sol. in water (1:1.7), alc. (1:1.3), or eth. Solutions turn brown, especially in the light; very rapidly if alkaline. Used externally (but dangerous) as 1 to 10 per cent ointment in skin diseases; and as 1 to 3 per cent solution to deodorize ozena and discharging wounds. The danger of poisoning and the black staining limit its employment. It is used like chrysarobin in psoriasis, lupus, ringworm and other parasitic skin diseases, and in hair dyes.

CREOSOTE AND GUAIACOL

The empyreumatic products of the distillation of wood smoke, and the creosote and tar which may be condensed from it, contain benzene derivatives of considerable antiseptic potency. Medicinal creosote is obtained chiefly from beechwood (first by Reichenbach, 1830). Its principal constituents are *guaiacol,* $C_6H_4.OCH_3.OH$; and *creosol,* $C_6H_3.OCH_3.CH_3.OH$. These are related to the cresols. They are more strongly antiseptic and antipyretic, and rather less irritant and toxic, than is phenol. Creosol should be superior theoretically, but practically does not differ sufficiently from guaiacol to offset its higher cost. Guaiacol constitutes from 60 to 90 per cent of the creosote, and shares all its properties, with the advantage of constant composition.

Uses.—Creosote and guaiacol are becoming obsolete. They were employed in *tuberculosis,* having been introduced especially by Sommerbrodt, 1887; but the clinical benefits are not definite, and the laboratory results are quite negative (L. M. De Witt *et al.,* 1920). Hospitalized patients with pulmonary tuberculosis show no improvement when treated with calcium creosotate, and no change in the sputum or expectoration. Neither the sputum nor the expired air contains the creosotate (E. J. Fellows, 1939).

Bronchitis and *pneumonia* were said to be benefited, especially by inhalation. When guaiacol is injected hypodermically, the major part is contained in the blood, liver and spleen, much less in the lungs and kidneys (Hofbauer, 1915). In *pleuritic effusions,* it hastens the absorption of the exudate when it is rubbed into the chest. As an *antipyretic,* guaiacol, 10 to 30 drops, dissolved in an equal volume of oil or alcohol, may be rubbed into the clean and dry skin of the abdomen for ten to fifteen minutes, thus avoiding intestinal irritation. It causes considerable diaphoresis, and has no advantage over other antipyretics. Guaiacol was classed as an *intestinal antiseptic,* but its action is difficult to demonstrate (Harris, 1912). Creosote water was sometimes given to check *gastric fermentation.* The *local anesthetic action* is utilized, especially *in dentistry.*

Administration.—In tuberculosis, creosote or guaiacol is given in the largest doses which can be tolerated without too much gastro-intestinal irritation, beginning with 1 drop and increasing to 5 or 10 drops, in extemporaneous capsules, three times daily after meals. If they are not tolerated, guaiacol carbonate should be substituted.

Poisoning by creosote resembles that by phenol, but the effects are less convulsive. The local actions are also similar. Death has occurred after 7 Gm. (Schulze, 1894). Hypodermically, guaiacol produces dangerous collapse and cardiac depression. The chief lesions in rabbits are nephrotoxic, mainly tubular, but also somewhat glomerular (Benoit, 1928). The *excretion,* as with phenol, is mainly in combination with glycuronic and sulfuric acid (Knapp, 1911) Guaiacol (but not its carbonate) causes, in very large doses, the appearance of an undetermined, viscous substance in the urine, which is said to be capable of obstructing the uriniferous tubules.

Guaiacol Carbonate is an insoluble ester which liberates guaiacol slowly and incompletely in the intestines. It was introduced to secure local intestinal antisepsis and avoid the taste and systemic toxicity; but too little is liberated to be effective. As much as 6 Gm. of guaiacol carbonate have been given to phthisical patients, as much as 75 Gm. (2½ ounces) to dogs, without producing toxic symptoms. With these large doses, a great deal of the substance is passed in the feces, without having undergone decomposition. *Other guaiacol esters* were also introduced, but have no advantage.

Thiocol is potassium guaiacolsulfonate, analogous to sodium phenolsulfonate. Like the latter, it has little effect. It is exploited as an expectorant, but it neither propels nor liquefies the mucus (roentgenologic observations), nor could any free guaiacol be demonstrated in the lungs even after large doses (Gordonoff and Wyss, 1933).

Preparations.—*Creosote* (Wood Creosote) consists of a mixture of phenols and derivatives, chiefly guaiacol and cresol, obtained during the distillation of wood tar, preferably that derived from beech. Almost colorless or yellowish, highly refractive, oily liquid having a penetrating, smoky odor; burning, caustic taste. Slightly sol. in water. Miscible with alc. and fixed or volatile oils. Dose, 0.12 to 0.25 cc., 2 to 4 minims; maximum, 0.5 cc., 8 minims. *Guaiacol,* $C_6H_4(OH)(OCH_3)$, is a nearly colorless refractive liquid, crystalline at low tempertaures. Odor, aromatic; sharp taste. Sol. in water (1:60 to 70); freely miscible with glyc., alc. or oils. Dose, 0.3 to 0.5 cc., 5 to 8 minims.

TAR

This is a complex product obtained by the destructive distillation of pine woods, especially Pinus palustris. It contains phenols and other aromatic derivatives, resin acids, acetic acid, and the like. Tar is strongly irritant to the skin; it is used in scabies and other parasitic skin diseases, and eczemas. It is said to be healing, antipruritic and drying, but has now been displaced largely by the less disagreeable naphthol and resorcin. Skin that has been treated with tar should not be exposed to the sun or to roentgen rays for several days.

Internally, pine tar has been employed in chronic bronchitis and cystitis, acting similarly to turpentine and copaiba. The official syrup is little more than a flavoring vehicle. Toxic doses of tar produce effects similar to those of phenol: vomiting, colic, diarrhea and collapse. Sezary and Wornes, 1928, reported acute leukopenia after application of juniper tar to the human skin.

Juniper tar has a more pleasant aromatic odor and is often substituted in dermatology. Crude *coal tar* (as 2 to 6 per cent ointment) acts similarly and is twice as effective as pine tar (C. J. White, 1921, 1927), but more malodorous. The odor and color may be partly removed by purification, but with some loss of therapeutic activity.

Oil of Tar.—When tar is subjected to redistillation, it can be separated into a fixed portion—pitch—consisting mainly of rosin; and a volatile portion which separates into *Oil of Tar* and pyroligneous (crude acetic) acid. Oil of tar consists of various coal tar derivatives, mainly cresols, guaiacol, phenol, xylene, toluene, and pyrocatechin. It also contains methyl alcohol and acetone.

PREPARATIONS.—*Pine Tar,* U.S.P. (Pix Pini), is a viscid blackish-brown substance obtained by the destructive distillation of Pine wood. Empyreumatic odor and sharp taste. Miscible with alc. and fixed or volatile oils, only partly sol. in water. *Pine Tar Ointment,* U.S.P. (Unguentum Picis Pini), contains 50 per cent of Pine Tar, 35 per cent of Yellow Ointment and 15 per cent of Yellow Wax. *Syrup of Pine Tar,* 0.1 per cent; average dose, 10 cc. *Juniper Tar,* U.S.P. (Pix Juniperi; *Oil of Cade, Empyreumatic Juniper Oil*), is a dark brown, clear, thick empyreumatic oil obtained by the dry distillation of the wood of Juniperus Oxycedrus; of warm, faintly aromatic and bitter taste. Used externally like pine tar. *Coal Tar,* U.S.P. (Pix Carbonis), a byproduct of the destructive distillation of bituminous coal, is employed as *Coal Tar Ointment,* U.S.P., containing 5 per cent of coal tar, 25 each of starch and zinc oxide and 45 of white petrolatum. *Solution of Coal Tar,* N.F., is to be diluted with 9 volumes of water, as a lotion.

CHEMICAL CARCINOMAS

Tar and Paraffin Epitheliomas.—Workers whose skin comes into frequent contact with coal tar and with crude paraffin may develop chronic dermatitis, eczema, eruptions and papillomas, which may eventually turn into true epithelioma. The susceptibility varies considerably. Pure paraffin does not produce this effect, but paraffinomas may sometimes take a cancerous direction.

Paraffin dermatitis and cancer were first described by Volkmann, 1895. The acute stage begins with eruptions and abscesses, *"wax boils."* These last several months and then pass into a chronic dermatitis, with seborrhea resembling psoriasis, pigmentation, dry fissures, horny thickening, resembling ichthyosis, and so forth. In the terminal stage, multiple warts or papillomas develop, turning finally to true epithelioma (Davis, 1915). The wax cancer affects only a fraction of the workers, and is therefore influenced by predisposition (B. F. Davis, 1920).

Chemical Carcinogenesis.—Cancerous tumors are produced by prolonged application of tar or certain of its constituents to the skin of mice, rats or rabbits, and also by hypodermic injections continued over long periods. The tumors are malignant, form metastases, and are transplantable to animals of the same strain (for over twenty passages; Z. K. Cooper *et al.*, 1944). They are inherent in the anthracene fraction of the tar (Norris, 1914). J. W. Cook and associates, 1935, isolated the pure carcinogenic substances and synthesized these and others. They are nitrogen-free aromatic hydrocarbons containing the phenanthrene ring. The most active are derivatives of benzanthracene 1.2, although this itself is not carcinogenic (Barry and Cook, 1934). Methyl cholanthrene, which is structurally related to desoxycholic acid and to cholesterol, is especially active. These substances are related in structure to the estrogenic hormones, and they are indeed mildly estrogenic, and vice versa, but the transposed actions require much more than the therapeutic dosage (W. Cramer and Horning, 1937).

Agents credited with producing occupational cancer include: arsenic, chromates, nickel carbonyl, dyes, ultraviolet rays, roentgen rays, radium, mesothorium, asbestos, crude mineral oils, pitch, tar, soot, anthracene oil, creosote, aromatic amino-compounds (aniline, naphthylamine, benzidine), substances from parasitic worms.

The carcinogenic activity, structure and chemical reactivity of the polynuclear aromatic hydrocarbons are reviewed by L. F. Fieser, 1938. The phenanthrene nucleus is not essential to carcinogenesis, for this is also produced by benzacridine (Barry, Cook *et al.*, 1935), and by triphenylbenzene and tetraphenylmethane (Morton, Branch and Clapp, 1936); but most of the active substances have a number of benzene rings linked together (G. M. Badger, Cook *et al.*, 1940). Some 150 chemicals, including inorganic substances, coal tar derivatives and dyes, were studied by B. T. Simpson and Marsh, 1931, in relation to spontaneous mammary cancer of mice, the greater number with negative results. *Benzene* is not carcinogenic; *oleic acid* occasionally produces benign tumors (Bottomley and Twort, 1934).

Development of the Chemical Cancers.—The scientific study of tar cancer was started by the observation of Yamagiwa and Ishikawa, 1915, that local cancerous changes are initiated by applying tar externally to rabbits' ears over long periods, half a year or a year. Tsutsui, 1918, showed that mice (and rats) are more suitable, with a larger proportion of takes. The incidence varies greatly with the strains of mice (Kreyberg, 1934); but there is no correlation with susceptibility to spontaneous tumors. The chemical tumors, like the spontaneous, can be transplanted successfully only into mice of the same strain (Andervont, 1934). The dosage has a limited influence in shortening the latent time (Dunning, Curtis and Bullock). With a single application of 20-methylcholanthrene, nearly half of the mice developed malignant tumors in thirteen to forty-two weeks (Cramer and Stowell, 1943). The interval between applications and cancer development is materially longer in long-lived animals, approximately proportional to the life span. The delayed actions of a single application set in long after the agent is no longer detectable at the site. The application must therefore have started a self-perpetuating abnormality that is transmitted through generations of cells (review, E. V. Cowdry, 1943). The effects of a second course of carcinogenic hydrocarbon are additive even after an interval of four months (Lavik *et al.*, 1942).

The precautions which must be followed in cancer experimentation on mice are reviewed by C. Voegtlin, 1937. Results obtained with one type of neoplasm can not safely be transferred to other types. Dibenzopyrene produces cancer in man as well in animals (review, F. C. Wood, 1937). Passey, 1938, obtained tar tumors in dogs. Not all strains of mice are susceptible to chemical *breast cancer;* those that are, are also susceptible to its spontaneous occurrence. Guinea pigs are much less susceptible than mice; rabbits are almost insusceptible. In man and primates, cancer production by these agents is not definitely established. The immunity of rabbits is probably due to detoxication; they oxidize dibenzanthrene to dihydroxy dibenzanthrene, which is not carcinogenic even for mice (C. P. Roads, 1942).

Experimental brain tumors, gliomas or meningeal fibrosarcomas are produced in eight to seventeen months by intracerebral implantation of pellets of 20-methylcholanthrene (Seligman and Shear, 1939) or of 3.4 benzopyrene in mice (H. M. Zimmerman and Arnold, 1943). *Pulmonary cancer* may be produced by injection of tobacco tar into the pulmonary parenchyma of rats (A. H. Roffo, 1943). Intrapleural injection of benzopyrene causes a condition resembling *leukemia* with malignant cells resembling monocytes, in 9 per cent of the injected mice (J. Furth and Furth, 1938). Leukemia, usually of lymphoid type, is also produced by painting the skin of mice with methylcholanthrene and other carcinogenic agents (review, J. Furth, 1946).

With direct application to the skin, the immediate effect is injury to the epithelium, which develops into cell proliferation, keratosis and chronic hyperemia (Cramer and Stowell, 1942). The cancer formation appears to be caused by direct stimulation of growth, rather than by irritation, for it may start distant from the site of application; thus in the *liver* after hypodermic administration of diamino anthracene, in the *lung* after dibenzanthracene (Andervont). *Dimethylamino azobenzene* (*"butter yellow dye"*) produces an orderly of sequence changes, with proliferation of bile ducts, liver parenchyma and supporting tissue, terminating in complex malignant tumors (E. L. Opie, 1944). (Its metabolites were studied by E. S. Stevenson *et al.*, 1942.) *Testicular* interstitial tumors may be induced in mice by administering triphenylethyline, 5 mg. weekly for fifty weeks or more (W. U. Gardner, 1943). Carcinoma develops in rats when 2-acetaminofluorene (*"AAF"*) is added to their diet (De Eds and Wilson, 1946). Dibenzopyrene and methylcholanthrene produce tumors in any organ in which tumors are known to occur naturally, including the gastro-intestinal tract, kidney, bladder and lung. The result may be either carcinoma or sarcoma, or mixed, according to which type of cells happens to yield and form a new race. Once started, the characteristics are retained; for instance, for over 440 generations of mice transplants. "The grafted tumors are merely a race of cells under cultivation" (Wood, 1937), a permanently altered race originating from a previously normal race (W. H. Lewis, 1935). The rate of growth of the tumor cells in tissue cultures correlates with their growth in the animals (Ludford, 1934).

Protozoa subjected to prolonged exposure to polycyclic hydrocarbons or other blastogenic agents, develop increased viscosity of the cytoplasm which interferes with division and results in morphologic abnormalities, similar to those of cancer cells, which are then perpetuated indefinitely in the progeny (J. C. Mottram, 1942, 1944). Continued exposure of many successive generations of protozoa or bacteria increases their susceptibility to its toxic actions (R. R. Spencer and Melroy, 1942). Methylcholanthrene has marked effects on *yeast cultures,* increasing the total growth by a third, with the appearance of many giant cells, after two months (C. W. Dodge, 1937). The photosensitivity of paramecia is increased by cholanthrene and several other carcinogenic agents, in dilutions greater than with any noncarcinogenic light sensitizer (Doniach, 1939). Light rays have some restraining effect on the development of benzopyrene tumors in mice (J. J. Morton *et al.*, 1940). In *higher plants,* the carcinogenic chemicals induce the formation of numerous adventitious roots on the stems of tomato and nicotiana (Kisser and Lindenberg, 1940); but nothing analogous to neoplasm; plant tumors appear to require the constant stimulation of a living parasite (M. Levine, 1942).

Anticarcinogenic Actions.—Certain dyes, Nile blue and methylene blue, when fed to rats, diminish the incidence of liver cancer from ingestion of O-aminoazotoluene (M. Hashida, 1941; S. Ito, 1941); similarly β-sitosteral with "butter yellow" (Sato and Morigami, 1941). *Plant hormones,* if permitted to act on minced tumor before its inoculation into mice, markedly decrease the number of takes and the subsequent growth rate; but if the tumor is already established, it is not affected by hypodermic injection of the plant hormones (B. E. Kline and Rusch, 1943).

Distant Effects of Coal Tar.—Rabbits to whose ears coal tar was applied once or twice a week, and which were killed after seven to twenty days, showed focal necrosis of the liver, ascites, edema of the subcutaneous tissue, fatty changes in the myocardium and liver, degeneration of the bone marrow, and emaciation (C. H. Hu and Wu, 1936). Oral administration of methylcholanthrene and of benzopyrene to rats decreases the rate of growth. This is counteracted by cystine, methionine and glutathione (J. White and White, 1939). *1.2.5.6 dibenzanthrene,* when introduced into the tail tissue of young rats so as to produce continued absorption, causes progressive inhibition of growth, resulting in permanent dwarfing (H. Alapy, 1941).

Bladder Tumors of Aniline Workers.—A high incidence of hemorrhagic cystitis, recurrent papillomas and cancers of the urinary bladder was reported by Rhein, 1895, in workers employed in the manufacture of aniline dyes, especially fuchsin, benzidine and naphthohydramine. H. Curschmann, 1920, estimated the incidence as high as 1:500. Lessenberger, 1912, found it thirty-three times as high as in nondye workers. People living in the vicinity of the factories do not show an abnormal cancer rate. The tumors are discovered from two to thirty-six years after starting the employment (Nassauer, 1919; Schwerin, 1920; Oppenheimer, 1920). The average is about twelve years. Half to two-thirds become carcinomatous (Gehrmann, 1936). Once noted, the tumors progress rapidly and the prognosis is unfavorable, even with radical operations. The effect appears to be due to the nitro and amino groups of aromatic intermediates (A. Mueller, 1933). Suspicion attaches especially to phenyl hydroxylamine, a metabolic decomposition product of aniline which irritates the bladder even in high dilutions.

Experimental Bladder Tumors.—Papillomas and cancerous changes can be produced by the introduction of pellets of equal parts of coal tar, scarlet red and paraffin into the bladder of rats (Maisin and Picard, 1924; Watanabe, 1934), and by the long-continued hypodermic or oral administration of commercial betanaphthylamine ($C_{10}H_4NH_2$) to rabbits or dogs (Perlmann and Staehler, 1933; Hueper, Briggs and Wolfe, 1938). It is conceivable that the effect may be due to impurities (Voegtlin, 1938). Prolonged administration of this drug also causes blood destruction, degeneration of the renal tubular epithelium and of the hepatic parenchyma (Ranta, Leming and Blood, 1938). 2-acetyl-aminofluorene, when fed to mice for fifty-two weeks, results in epithelial tumors in the urinary bladder of about half of the animals; also in neoplasms in the liver and uterus and other organs of rats and mice (R. H. Wilson *et al.*, 1941; E. P. Armstrong and Bonser, 1944).

Bladder hyperkeratosis and papillomas may also be produced in rats by administering azotoluene with a diet of rice flour (J. P. Strömbeck, 1946).

BENZENE

Benzene (benzol), C_6H_6, is an important industrial poison, generally as vapor, from its extensive use as a rubber solvent, motor fuel, and so forth. It acts acutely as a lipolytic narcotic and asphyxiant convulsant. Chronic poisoning involves the bone marrow, decreasing first the white and then also the red corpuscles. It has been used in leukemia, but is unreliable and dangerous. It is somewhat antiseptic. It causes local irritation; subcutaneous injection results in edema, induration and abscess (Chassevant, quoted by Ellinger, 1923). Benzene must not be confused with "Purified Benzin," U. S. P., which is a gasoline fraction.

Fate.—Benzene is partly oxidized in the body to phenol (15 to 30 per cent), catechol and quinone and excreted as phenolsulfates (Baumann and Herter, 1877); a part is completely destroyed to muconic acid (Jaffe, 1909), and a considerable portion is excreted unchanged by the lungs. The brain and spinal cord contain more than other organs (Joachimoglu, 1915).

Acute Benzene Poisoning.—Fairly large doses are tolerated by mouth; 9 to 12 Gm. have caused serious collapse (Perrin, 1861; Averill, 1889). The acute symptoms are restlessness, excitement, high rise of temperature, narcosis, and death by paralysis of respiration. Sublethal doses are followed by good recovery. The technical article is somewhat more toxic than the pure (Lehmann, 1911).

Acute clinical poisoning by benzene vapor occurs by absorption through the lungs. *Small amounts* produce euphoria and inebriation similar to that of alcohol. This passes rather rapidly into drowsiness, giddiness and motor incoordination which interferes with escape. Fuehner found benzene about as narcotic as chloroform. Vomiting may set in, with collapse, pallor of the face and cyanosis of the extremities. Larger amounts cause twitching and convulsions, passing into paralysis. The respiration becomes slowed, the blood pressure falls, unconsciousness and coma supervene. Death may occur suddenly in the convulsions, or more gradually in coma. The *necropsy findings* are those of suffocation, including edema of the cerebral meninges and lungs. The blood remains fluid for a long time; there are often small hemorrhages in various organs. Patients who recover sometimes develop skin changes (Lewin, 1907; Wolf, 1911; Heffter, 1915). *Acute poisoning in animals* by pure or impure benzene shows the same symptoms, the impurities having but little effect, so that "crude" benzene is less toxic than the "pure" and "commercial"; these are about equally toxic for dogs and guinea pigs (Schrenk, Yant *et al.*, 1940). *Ventricular extrasystoles* set in promptly. With fatal doses these pass into ventricular tachycardia and fibrillation. This may be prevented by the injection of mecholyl, not by quinine. There is also peripheral paralysis of the blood vessels (Dautrebande, 1933; Nahuen and Hoff, 1934). *Epinephrine,* 0.02 mg. per Kg., injected intravenously into dogs inhaling benzene, generally evokes ventricular fibrillation. This "*benzol-adrenalin test*" has been used by Wégria and Nickerson, 1942, to confirm the protective action of quinidine.

Acutely Toxic Concentrations.—Slight symptoms occur after several hours' exposure to 1500 to 3000 parts per million of air. The maximal concentration that can be inhaled for an hour without serious disturbance is 3000 to 5000:10^6; 7500:10^6 is dangerous in one-half to one hour. With 19,000:10^6 (2 per cent) death occurs in five to ten minutes. The toxic concentrations were determined on cats by Bamesreiter, 1932. With rats, narcosis occurs above 0.1 per cent (volume); 0.16 per cent is fatal in less than six hours (H. Taylor, 1939).

Chronic benzene poisoning may result from therapeutic oral administration, or from inhalation in the industries. It constitutes an important industrial hazard. Its history and symptomatology were reviewed by Winslow, 1927, for the National Safety Council. A group of papers appeared in the Journal of Industrial Hygiene, 1939. Workers gradually (after two or three months or later) develop leukopenia, alpastic anemia and purpura haemolytica, without other marked symptoms. They generally recover slowly but completely when removed from exposure. L. J. Goldwater, 1941, observed the frequent occurrence of anemia, macrocytosis and thrombocytopenia in rotogravure workers, but leukopenia and prolonged bleeding and coagulation time were exceptional. The susceptibility varies greatly, and some workers show no apparent effects (Legge, 1920). Young persons and especially pregnant females are said to be more susceptible; but, women in general are not more susceptible. Corresponding phenomena are produced by dilute vapors in animals (Santesson, 1897; Selling, 1912). Their susceptibility increases with repeated exposure, thus explaining the deferred outbreak in workers. The effects are greatly diminished by dilution, *i. e.*, by liberal ventilation, and this is indispensable to protection. Contact of the liquid benzene with the skin adds materially to the danger. Leukocyte counts and determinations of the urinary sulfur partition should be made periodically on exposed workers, to detect the poisoning at its inception. The toxicity of the vapors of pure benzene is as high as that of the impure, if not higher (Pugliese, 1922). It is also the dominant toxic ingredient in benzene-toluene-xylene (Svirbely *et al.*, 1944).

Mechansim of Action.—The benzene effects are attributed to destruction of leukocytes in the circulating blood, and to damage of the bone marrow, lymph glands, spleen and the whole hematopoietic system. The formation of blood platelets is first stimulated, then depressed (Duke, 1913). The uric acid is not increased, and this speaks against destruction of leukocytes. Pappenheim, 1913, believed the decrease to be only apparent, asserting that the leukocytes accumulate in the dilated capillaries of the liver and other internal organs. He found marked hepatic and renal lesions in rabbits after repeated large doses. Duke, 1915, attributed the platelet changes to irritant, then toxic, action on the bone marrow. This shows the reddish-yellow gelatinous appearance of aplastic anemia in autopsies of patients with chronic benzene poisoning (bibliography, Engelhardt, 1931). The human series of Mallory, Gall and Brickley, 1939, ranged from severe hypoplasia to extreme hyperplasia.

Blood Changes in Animals.—Subcutaneous injections of benzene (2 to 40 cc.) into rabbits or dogs produce death in three to twenty days, with marked destructive changes in the hematopoietic organs, especially the myeloid tissue. There is a corresponding diminution of the leukocytes and blood platelets. With large doses, the platelets show a preliminary increase in rabbits, not in dogs (Duke, 1915). Recovery may be followed by a second fall (Weiskotten *et al.*, 1916). With rabbits, hypodermic injection of small doses (0.01 Gm. per Kg.) daily for eighty-five days produced transient leukocytosis, terminal anemia, marked thrombosis, decreased resistance, degenerative changes in leukocyte structure (G. Bayer, 1933). *Erythrocytes* decrease progressively in number; abnormal forms appear, including punctate basophilia (W. D. Paul, Friedländer and McCord, 1927), but no reticulocytes. The acute blood destruction causes increased pigment deposition in the liver and spleen. Rabbits exposed for two hours to 1 per cent vapor respond with immediate fall of erythrocyte count, by 25 per cent, followed in two or three days by a sharp rise, and then a second drop, which may go below the first; and finally a slow return to normal, generally in two weeks (E. J. Robinson and Climenko, 1938).

Hemorrhages, similar to purpura, into the skin and mucosae, including the stomach and intestines, occur frequently in chronic benzene poisoning. Uterine hemorrhage may be so severe as to cause death. The bleeding also favors fatal infection. The production of antibodies is diminished (Hektoen, 1916). The hemorrhages are due to decreased clotting power of the blood, involving lowered prothrombic content (Hurwitz and Drinker, 1915), thrombopenia and leukopenia, and damage to the endothelial cells (Dautrebande, 1933).

Dermatitis.—Chronic exposure to benzene may lead to extensive eczema, with irritation of the skin follicles, cornification of the sebaceous glands, increased pigmentation and keratosis. This may involve damage to the cornea.

Neuritis develops in some cases, and may include retrobulbar optic neuritis and blindness.

Safety Limits of Benzene Exposure.—The National Safety Council suggested 100 parts per million of air as a safe limit; 75 parts are distinctly safer, and even this may be fatal to susceptible persons (Bowditch and Elder, 1939; F. T. Hunter, 1939). Poisoning occurs in factories with air concentrations of 200 to 5000 parts per million. The *partition of sulfur in the urine* appears to be a better and safer criterion of excessive exposure because it is more individualized. Normally, 80 to 100 per cent of the urinary sulfur exists as inorganic sulfate. On exposure to benzene, this conjugates with part of the sulfate, and the ratio of inorganic sulfate is correspondingly reduced to 25 per cent and less often to 0. The reduction shows long before the blood changes, and if excessive exposure is promptly corrected, rapid recovery results (H. H. Schrenk *et al.*, 1936). *Low protein diet* renders the liver of animals more susceptible to the toxic effects; leukopenia is greater on high fat diet (T. W. Li *et al.*, 1944, 1945).

Risk of Industrial Poisoning from Benzene Derivatives.—H. F. Smyth, 1931, claimed that the risk of accidental poisoning is slight with substances whose M. L. D. lies between 0.1 and 0.25 Gm. per Kg. of body weight, if the toxicity is realized and proper precautions are taken.

Use in Leukemia.—The destructive action of benzene on leukocytes led to its introduction by v. Koranyi, 1922. Numerous reporters (Kiralyfi, 1912; Billings, 1913; Morawitz, 1914; and others) described more or less favorable, but rather inconstant, results. The changes are noticed only after continued administration (5 to 15 minims, four times daily), often requiring some weeks. The leukocyte count falls, more profoundly and persistently than with arsenic, but never to normal, as in x-ray treatment. In a considerable number of cases, especially the advanced, the benzene is unsuccessful. In others, toxic effects supervene, and this has discouraged its use; ordinary doses cause eructations, but the appetite is not disturbed. There may be some dizziness, sometimes bronchitis. Occasionally, late symptoms of chronic benzene poisoning develop, which may be fatal (Neumann, 1913; Klemperer and Hirschfeld). It is therefore advisable to discontinue the benzene as soon as the leukocytes start to decline (Kiralyfi, 1913), or at least when they have fallen to 20,000. Liver, kidney and intestinal disturbances contraindicate benzene (Hahn, 1914).

METHYLBENZENES: TOLUENE AND XYLENE

Toluene (toluol), $C_6H_5CH_3$, and xylene (xylol), $C_6H_4(CH_3)_2$, resemble benzene in their actions (Baumann and Herter, 1877), and have about the same acute toxicity; but they are much less deleterious under ordinary factory conditions, especially to the bone marrow (Halsgren, 1926). *Toluene* is used in paints, where it has largely displaced benzene. It is employed as a laboratory antiseptic, especially to preserve ferments. It is more irritant than benzene, somewhat more narcotic in lower concentrations, and has considerably less effect on the blood picture. *Toluene fumes in industry* produce irritation of mucous membranes, depression of the central nervous system, and depression of the bone marrow. Susceptibility differs markedly. Enlargement of the liver and macrocytosis are usually the first signs of chronic industrial poisoning. They are followed by decrease of red cells, usually moderate, and lymphocytosis. Leukopenia is exceptional. Exposure of men for eight hours daily to 200 parts per million produces some impairment of coordination and reaction time. The inorganic sulfate in the urine is not affected, in contrast to benzene. The more susceptible individuals should not be employed. Treatment would consist in blood transfusion followed by liver and iron administration (R. H. Wilson, 1943; von Oettingen *et al.*, 1942; L. Greenberg *et al.*, 1942). *Xylene* is used extensively in printing. A 25 per cent ointment in equal parts of hydrous woolfat and petrolatum is effective against pediculosis pubis (C. Ferguson, 1930). *Cumene*, isopropyl benzene, a higher homologue of the benzene series, produced slow and prolonged narcosis. It is toxic in considerably lower concentrations than benzene or toluene, but its higher boiling point (152° C.) makes it easier to control (H. W. Werner *et al.*, 1944). "*Solvent naphtha*," consisting chiefly of xylene with small amounts of toluene and thiophene, has largely taken the place of benzene in industry.

Fate.—A methyl group is oxidized in the body. Toluene is thus converted into benzoic acid, which is excreted as hippuric acid. Xylene is oxidized to toluic acid, $C_6H_4CH_3COOH$, which pairs with glycocoll to toluric acid.

NAPHTHALENE

This represents the union of two benzene rings, $C_{10}H_8$. It occurs as a colorless, crystalline powder, of coal tar odor and hot taste. It is practically insoluble in water, soluble in alcohol (1:13).

Uses.—It is employed as insecticide (moth balls), but is not very potent (W. E. Fleming and Baker, 1934). It has been used as antiseptic dusting powder in skin diseases and as intestinal antiseptic and anthelmintic, especially against oxyuris. *Dose*, 0.1 to 0.5 Gm. (2 to 8 grains). For children, 0.05 Gm., 1 grain, at one and one-half years; to 0.2 Gm., 3 grains, at twelve years, three times daily. Fumigations have been tried against pertussis.

The **toxicity** is usually rather low, because but little is absorbed, the greater part being eliminated unchanged by the feces. That absorbed is excreted as naphthol, naphthoquinone, and the like, and produces renal and vesical irritation and hemorrhage, and damages the blood-forming organs, resulting in anemia (S. Mayer, 1920). However, the absorption is sometimes greater (Kaminer, 1920), especially when it is vaporized, and orally in the presence of oil: 2 Gm., administered in the course of two days, proved fatal to a six-year-old child (Prochownik, 1911). Heine, 1913, reported poisoning in a woman after 2.8 Gm., distributed over three days. *Milder cases* show headache, nausea, vomiting, profuse perspiration, hematuria, slight edema, optic neuritis; sometimes damage to the cornea, retina and lens, similar to naphthol (Takamura, 1913). The cholesterol content of the tissues may be altered (Michail and Vancea, 1927).

Naphthalene Cataract.—Lens changes appear within one to three days after daily administrations of naphthalene to rabbits by stomach tube, 1 Gm. per Kg. of body weight. They progress so that the lens becomes completely opaque within twenty days. The initial lesions and the course resemble those of human cataract. The mechanism is not known, except that the glutathione content of the lens diminishes, and this is probably concerned in the lens metabolism. There are also severe lesions of the retina and signs of general intoxication (review, M. C. Bourne, 1937). All these effects are more marked in rabbits on a diet of bran, carrots and oats; they may be entirely suppressed by adding cabbage to the feed (Bourne, 1933).

Hydrogenated Naphthalenes.—Tetrahydronaphthalene (tetralene, $C_{10}H_{12}$) and decahydronaphthalene (decalene, $C_{10}H_{18}$) are used as solvents for resins and fats in the dye and lacquer industry, and also in motor fuel mixtures. Their toxicity is relatively low (Leschke).

Pentachlorinated naphthalene, used as coating of wire cables, produces papular rash in exposed skin. The dust and the fumes may cause fatal acute atrophy of the liver (L. H. Cotter, 1944; E. Collier, 1943).

NAPHTHOL

Alpha- and betanaphthol, $C_{10}H_7.OH$, are phenols, formed by the introduction of an OH group into naphthalene. *Betanaphthol* is the less toxic of the isomers. It is more germicidal than phenol. It is almost insoluble in water, and is employed as an ointment in alopecia (1 to 2 per cent), psoriasis, acne, parasitic skin diseases, pruritus, 3 per cent for adults, 1 per cent for children. A 10 per cent ointment is keratolytic. Caution is necessary lest the action become too violent and cause peeling which may be followed by persistent pigmentation. Betanaphthol is also employed to deodorize ozena. Internally, it is used as an intestinal antiseptic and anthelmintic. It is effective in hookworm disease, but inferior to thymol (Freeman, 1908). The local irritation and toxicity may be lessened on the salol principle, by transforming it into esters.

Toxic Effects.—Naphthol is especially irritant to the kidneys. Severe nephritis has been caused by its absorption from the intact skin in the therapeutic dose (Kaposi, 1881; Baatz, 1894). Death has been reported from its external application in scabies (L. Burger, 1919). It is especially contraindicated in the presence of renal diseases. Changes in the retina and opacity of the lens have also been described after its use (*e. g.*, Howe, 1913).

Betanaphthol, U.S.P. (*Naphthol,* B.P.), $C_{10}H_7OH$, occurs as colorless or buff-colored, crystalline laminae or powder; faint phenol odor; pungent taste. Very slightly sol. in water (1:1000); very sol. in alc. (1:0.8) and in oils, glycerin and alkalis. Dose, 0.25 Gm., 4 grains; against hookworm, 1 to 4 Gm., by special technic (Freeman, 1908).

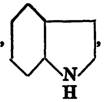
Beta-tetralol, 1,2,3,4 tetrahydrobetanaphthol, which is used as insect repellant, produces cataract in rats in four to six weeks, if 1 to 2 per cent is added to their diet (O. G. Fitzhugh, 1946).

PARADICHLOROBENZENE

This is a by-product of the manufacture of picric acid. It resembles naphthalene in physical properties, and is chemically indifferent. It is a potent insecticide (Konantz, 1918). It is also toxic to worms. Oral administration to dogs produces no apparent deleterious effect, even in the dosage of 1 Gm. per Kg. (Sollmann, 1919). It is inferior, however, to carbon tetrachloride, and its use on stock animals taints the meat (Dikmans, 1927). It is used as a moth repellant. Several young workers exposed to this vapor for one or two years developed toxic hepatitis and cataract. Inhalation of fatal concentrations by animals results in vacuolization and necrosis of the liver cells, but no changes were observable in the lens (Berliner, 1939).

Orthodichlorobenzene is used extensively as solvent for lacquer, and in protecting wood against termites. *Orthodichlorophenol* is also employed as wood preservative. Both may produce vesication (Downing, 1939). The chlorophenols are more toxic to rats by mouth than hypodermically. They produce restlessness, increased rate of respiration, rapidly developing motor weakness, tremors, clonic convulsions, dyspnea, coma and death (W. B. Deichmann, 1943). *Para chlorophenol* is a potent bactericide for gram-negative organisms, effective in clinically safe concentrations. F. L. Meleney *et al.*, 1946, recommended an ointment containing P-chlorophenol, 0.25 per cent, and penicillin, 250 units per Gm., in a water-soluble carbowax and propylene glycol base.

INDOLE

This substance, benzopyrrole, , has a peculiar action on the motor elements of the spinal cord and especially the pons, in rabbits and mice, so that any impulses from the higher centers result in fascicular twitchings and clonic convulsions (Feinberg and McCulloch, 1944). Intravenous injection into dogs produces brief apnea followed by hyperpnea; immediate fall of blood pressure; increased mucous and salivary secretion, convulsive movements, and death by cardiac dilatation (Ets and Feinberg, 1942). The toxicity of indole acids, according to A. Berthelot and Dieryck, 1939, is considerably less than had been reported by Anderson, Shimkin and Leake, 1936, the difference being due to the toxicity of the solvent. In frogs, the action is more on the cord than on the pons (Yanai, 1935). Methylindoles paralyze the central nervous system in frogs, especially the sensory cord.

Dichlorophenol indophenol, the dye used for estimating ascorbic acid, is reported to be carcinolytic: Infiltration of human cancers with N/400 solution, twice daily for two weeks, was followed by disappearance of cancer cells and formation of fresh granulation tissues (H. Rotter, 1939). Confirmation should be awaited. *Phenol-indophenol dyes* produce pallor in amphibian larvae by inhibiting the tyrosinase in their melanophores (F. H. J. Figge, 1938).

Indole Acids as Phytohormones.—Indolyl-3-acetic acid (and the corresponding propionic and butyric acids, and a number of other ether-soluble unsaturated fatty acids) act as "*hetero-auxins*": dilute solutions ($1:10^8$) markedly increase the growth of plants by stimulating them to synthesize solid material (reviews, K. V. Thimann, 1946; P. W. Zimmerman, 1943). Haloid derivatives of weak organic acids are especially effective—dichlorophenoxyacetic acid is three hundred times more potent than indolebutyric acid (Zimmerman and Hitchcock, 1942).

Auxins occur naturally in plants, most abundantly in the developing buds and young leaves where they are produced. The naturally occurring auxins are easily oxidized, and leaves contain enzymes for their destruction.

Auxins have several distinct actions: (1) They intensify photosynthesis (Cholodny and Gorbovsky, 1939); (2) they promote elongation of the plant; (3) they stimulate root growth, so that seeds start roots earlier, and rooting may be produced in unusual locations on the plant (Zimmerman and Hitchcock, 1935). Thiamine and its fraction thiazole are essential to root growth and enable tomato roots to grow without tops in culture solutions (W. J. Robbins and Schmidt, 1938); (4) they induce fruit formation in the ovary; (5) they inhibit the growth of lateral buds; (6) they inhibit autumnal leaf fall; (7) higher concentrations are fatal to plants, much more so to broad-leaved plants than to grasses.

Indole acetic acid and a number of other auxins inhibit the growth of certain *bacteria,* but varying greatly with the species (R. J. Dubos, 1946).

Phytohormones are used in horticulture to stimulate the rooting of cuttings. Spraying of orchards reduces the premature dropping of fruit by half, and has become standard orchard practice. They are used extensively as *weed killers,* especially *2,4-dichlorophenoxyacetic acid* ("2,4-D") and the trichlorocompound ("2,4,5-T"). These are beneficial at 10 per million, but at 100 to 1000 ppm they stimulate abnormal growth and kill the entire deep root system when applied to the foliage. They are highly selective; tomato plants are killed by spraying with 100 ppm of 2,4-D. It is nonirritating to the skin and relatively nontoxic to animals. Fish survive concentrations that kill water hyacinths. Sodium dinitro-ortho-cresylate ("sinox"), a yellow dye, also kills broad-leaved annual weeds with little effect on grass (review, E. M. Hildebrand, 1946). The estimation of phytocidal action is outlined by H. R. Offord, 1946.

Beta-indolylacetic acid, $1:10^7$, suppresses the germination of clover, but it has a much lower *toxicity in soils,* where it is decomposed by the soil bacteria. The 2,4-dichlorophenoxyacetic acid is toxic to clover and sugar beet with $1:10^6$ in soil, and retains its toxicity much longer (Nutman *et al.*, 1945).

In animals, parenteral administration of *2,4-dichlorophenoxyacetic acid,* 150 to 200 mg. per Kg., produces myotonia lasting eight to twenty-four hours. Repeated injections did not produce any functional or morphologic changes, with the doses studied (N. L. R. Bucher, 1946).

Phytohormones do not affect the growth, development and estrus cycle of rats, or the incubation of chicken eggs (W. S. Dye *et al.*, 1944).

QUINOLINE

Quinoline, C_9H_7N, is derived from naphthalene by the substitution of a N for a CH group. It is highly toxic and strongly antiseptic (Donath, 1881). In rabbits, the hypodermic or intravenous injection of 0.2 Gm. per kilogram produces retinitis, similar to that from naphthalene; the lens, however, remains clear (Jess, 1916).

Oxyquinoline Sulfate, $(C_9H_7ON)_2.H_2SO_4$, is strongly bacteriostatic, but feebly germicidal. It seems to be nontoxic and is used as an antiseptic lotion for mucous membranes and the like, under the name of **chinosol.** Its fate was studied by Brahm, 1899, and Grabbe, 1928. It is rapidly absorbed from the intestines of dogs, and as rapidly excreted by the urine (almost completely conjugated with sulfate; a small part free) and by the bile. Several iodated derivatives are used as effective amebicides in dysentery, especially Vioform and Chiniofon (Yatren); see Index. Various *dioxyquinoline* derivatives were investigated by Mancini, 1932.

ANILINE

Aniline, $C_6H_5NH_2$, is used extensively in the arts and gives rise to industrial poisoning, with methemoglobin formation, headache, weakness, dyspnea, cyanosis, convulsions and psychic disturbances. Acute effects on dogs involve methemoglobin formation; and results of the anoxia are essentially on the central nervous system and heart (B. B. Clark *et al.*, 1943). Its excretion was studied by Rambousek, 1913.

Chronic poisoning sometimes develops vesicular miliaria and other skin eruptions. The blood changes are less marked than in the acute. It has been asserted that the *methemoglobin formation* is increased by alcohol, clinically, and this has been confirmed in cats. The explanation is not clear. It is not due to more rapid absorption or to increased oxidation of the aniline (Schwedtke, 1938). It has been suggested that impurities may play a large share in industrial poisoning (review, Luce and Hamilton, 1916).

Heart; Curare Action.—Aniline and its methyl derivatives (*toluidine* and *xylidine*) are toxic to the *frog heart*, increasing the chronaxia markedly (R. Bonnet and Lelu, 1933). They have little effect on the frog sciatic nerve, but a strong curare action (Bonnet, Faye and Monrot, 1933).

Xylidine, with moderate concentrations, produces jaundice and fatty liver in dogs. Prolonged administration results in precirrhotic changes, with parenchymal injury, but with unimpaired reticulo-endothelial function (Svirbely, Monaco and Alford, 1946).

Shoe-Dye Poisoning.—Black dyes for leather commonly contain aniline oil and nitrobenzene, and numerous poisonings have been caused by recently dyed shoes. They are characterized by marked cyanosis, with blue lips and ears, and gray face, noticeable in one to three hours, often preceding the subjective symptoms of anoxemia: faintness, vertigo, headache and nausea. More severe cases resemble ordinary acute aniline and nitrobenzene poisoning. Polyuria and severe thirst are frequent. Fatalities are rare and recovery is fairly rapid (Stifel, 1919). The effects are probably due to aniline, for nitrobenzene is not so readily absorbed through the skin (Schwedtke, 1938).

Aniline dye poisoning with cyanosis has been reported in infants from skin absorption of the dye from freshly stamped pads (Graubarth *et al.*, 1945).

PHENYLHYDRAZINE

This is employed as the hydrochloride, $C_6H_5NH.NH_2HCl$, against polycythemia vera. It produces striking and peculiar changes in the blood picture, which may advance to profound anemia.

The effect is not shared by its components, hydrazine and phenyl, which as such do not alter the blood picture (E. V. Allen and Page, 1930); and the action and its mechanism are quite different from those of benzol. The latter produces aplasia of the bone marrow and spleen, with decrease of the leukocytes and erythrocytes and platelets. Phenylhydrazine, as studied in animals, has little effect on hematopoiesis; it does cause hyperplasia of the spleen and slight hyperplasia of the leukoblastic elements of the bone marrow, but it has no primary effect on the erythroblastic elements or on the platelets, and the reticulocytes tend to increase. Its anemia is due essentially to hemolysis of the mature red cells, but the mechanism is obscure (Evenson, 1938). Destruction of hemoglobin occurs presumably within the red blood cells, since these contain *basophilic masses;* similarly with other hydrazines and hydroxylamines (O. Warburg *et al.*, 1931). The effect is not altered by removal of the spleen (Giffin). The hemolysis results in increased deposition of iron in the liver and spleen, in bilirubin in the blood, and in large amounts of urobilin and urobilinogen in the urine, sometimes also hematoporphyrin. The urine may turn darker on standing. The nitrogen of the urine and blood is high, the blood calcium is low.

The *therapeutic response* is satisfactory in somewhat over half the cases of polycythemia. It becomes manifest after some days, with rise of the leukocytes to 50,000 or more, followed by a decline of hemoglobin and erythrocytes, with disappearance of the other symptoms. The effects are cumulative and continue for a week or two after the administration has been stopped, partly because the excretion of the drug is slow.

Phenylhydrazine hydrochloride is *administered* by mouth in capsules, 0.2 Gm. (3 grains) daily, for three to

four days, then 0.1 Gm. daily until the leukocytes rise, or until the hemoglobin falls below normal, usually in three to four weeks, when a total of 1 to 3 Gm. have been administered (Brown and Giffin estimated that 1 Gm. of phenylhydrazine would reduce the hemoglobin by about 6 Gm.). The administration is suspended temporarily if immature red cells increase. If the effect is incomplete another course may be given after an interval of a week or two, as a precaution against cumulation. After the normal level is reached it may be maintained with smaller doses which may be tried out for each patient, using 0.1 Gm., one to three times per week. Stealy and Sumerlin, 1944, reported a patient whose polycythemia was kept under control for eleven years without bad effects. (Acetyl phenylhydrazine, "Pyrodin," has also been used in polycythemia.) *Untoward symptoms* appear as a rule when the total dosage of the course exceeds 2.5 Gm.: jaundice, anorexia, nausea, slight bladder irritation, pruritus (Giffin and Conner). Others have reported dermatitis (eczema, erythema nodosum and papulosum), excessive hemolysis and increased tendency to thrombosis. On account of this, phenylhydrazine is generally avoided when patients are confined to bed or are elderly with advanced arteriosclerosis, as also in diseased conditions of the heart, kidney or liver.

Industrial poisoning has occurred, usually in minor degree, from repeated contacts with the skin whence it is more readily absorbed than from the digestive tract. It causes local irritation (pustules, edema) and systemic effects: headache, diarrhea, anorexia, lassitude, pallor, loss of weight; the urine may contain protein and blood.

Toxic Effects in Animals.—Doses proportionate to the clinical, continued for eight months, did not produce untoward effects in dogs (Allen and Giffin). Larger doses (rabbits or guinea pigs, 0.04 to 0.12 Gm. hypodermically) cause acute poisoning, with hemolysis, fall of blood pressure, asthenia, increased respiration, fall of temperature, albumin and urobilinogen in the urine (Lande *et al.*). With fatal doses, especially intravenous, necropsy shows hepatic swelling, degeneration and necrosis, pneumonic infiltration and degenerative changes in the other viscera (Wells; Underhill). Phenylhydrazine produces rapid formation of *methemoglobin* and other unidentified hemoglobin derivatives in life, more slowly in the test tube. When it is injected hypodermically into a rooster, the color of the comb turns to brownish-black in two or three minutes (L. Lewin, 1901). The hemoglobin of frogs forms a peculiar "hemoverdin."

NITROBENZENE

Nitrobenzene, $C_6H_5NO_2$, is used extensively in the manufacture of aniline. Its odor resembles that of hydrocyanic acid. It is employed in cheap perfumery and soaps, under the name of Artificial Oil of Almonds or Oil of Mirbane, but it is highly toxic; 1 Gm. may be fatal.

The *toxic symptoms* are usually rather delayed, sometimes for twelve hours, and are said to be accelerated by alcohol. They resemble those of aniline poisoning, and consist in nausea and prostration, burning, headache, intense cyanosis from methemoglobin, beginning in the lips and spreading over the entire body, air hunger and increased heart action, vomiting with characteristic odor, sensory skin irritation, convulsions and coma, ending in death after a few hours. The prognosis is generally good even in severe cases; the mortality is about 20 per cent; but with prompt treatment, 30 cc. were survived (Zuccola, 1918). In protracted cases, temporary improvement and relapses occur. The methemoglobin persists for many days.

The cyanosis is a striking feature, the face turning almost black; the blood, when withdrawn, is also dark, owing to the formation of methemoglobin. The blood corpuscles undergo rapid and intensive destruction. The urine may contain hemoglobin, methemoglobin, porphyrin, urobilinogen, urobilin, albumin and casts. In case of recovery the anemia is followed by active regeneration, with marked hyperactivity of the bone marrow (Zuccola). Polycythemia to six or seven millions may develop. The other symptoms result largely from the asphyxia; but the motor centers are probably affected directly. The respiration and circulation undergo relatively little disturbance. The reported cases of nitrobenzene poisoning were reviewed by S. S. Adams, 1912. Nitrobenzene has been taken to produce *abortion*, but even large doses are ineffective (Spinner, 1917). *Treatment* of poisoning consists in evacuation and stimulation. No fat should be given. Transfusion of blood results in marked improvement (Zuccola).

Inhalation of Nitrobenzene Vapor.—The symptoms differ in detail with the species of animals. They generally begin three or four days after exposure, with vomiting and marked digestive disturbance; then loss of muscular coordination, generally starting with the hind legs; forced movements or extensor rigidity. Consciousness is preserved. Death occurs through respiratory failure (Dresbach and Chandler, 1917). The motor symptoms are of cerebellar type; histologic examination shows changes in the cerebellar Purkinje cells, while other nerve cells are unaffected (Dresbach and Chandler, 1918).

Subacute and chronic nitrobenzene poisoning shows icterus and cyanosis, the clinical picture resembling that of pernicious anemia. The liver damage may be fatal. Otherwise, the prognosis is favorable, but the blood regeneration is much slower than after acute poisoning.

Nitrotoluene presumably acts similarly to trinitrotoluene.

Methemoglobin production by aromatic amino and nitro compounds (aniline, nitrobenzene, etc.) occurs much more rapidly and readily in living man and many animals than in shed blood; and not at all in rabbits, even with fatal doses, although these form methemoglobin with nitrites. Apparently the methemoglobin formation is not due to the aniline and nitrobenzene as such, or to the final products of their metabolism, paraminophenol and nitrophenol, but to intermediate products, especially to phenylhydroxylamine, C_6H_5NHOH, or aminophenols (Heubner, Lipschitz). These are oxidized by the oxygen of oxyhemoglobin, and this process liberates active oxygen, which oxidizes the oxyhemoglobin to methemoglobin. This may again be reduced by more of the phenylhydroxylamine. Paradinitrophenol can transform a hundred times its equivalent of hemoglobin, so that the action is catalytic (Heubner and Lo-Sing, 1938). Differences in this metabolism may explain the differences in the process.

With acute nitrobenzene and aniline poisoning of dogs, methemoglobin appears in spectroscopic traces in one and one-half hours, becomes distinct in two and one-half hours and increases for about six hours (Dietrich, 1892). The methemoglobin percentage rises higher in the blood of splenectomized dogs than normally (Ray and Stimson, 1927), perhaps because the circulating blood is normally diluted with spleen blood, which is less exposed to nitrobenzene. Methylene blue, 1 to 2 mg. per Kg. intravenously, or 65 to 130 mg. by mouth every four hours, restores methemoglobin to oxyhemoglobin, clinically (A. F. Hartmann, 1938) and in animals (A. P. Richardson, 1939).

TRINITROPHENOL (PICRIC ACID)

The saturated aqueous solution is used *externally* as a dressing for burns and superficial wounds, weeping eczemas, and so forth, exerting anesthetic, antiseptic, astringent and protective actions, and stimulating the reproduction of epithelium, in contrast to most other antiseptics (Ehrenfried, 1911). It is less painful than tannic acid. Stronger alcoholic solutions are irritant and, when absorbed, become toxic. This may also occur when aqueous solutions or dusting powders are applied to large surfaces, so that it should only be used on small burns. *By mouth,* 1 to 2 Gm. produce severe poisoning, generally with recovery under treatment (Lewin). It stains the skin, conjunctiva and tissues yellow, even on systemic administration, simulating icterus. This may persist for two weeks after taking 1 Gm. The urine is colored a peculiar red (Walko, 1901).

The toxic effects were investigated on dogs by Rapp and Foehr, 1827. Braconnet, 1830, introduced it against intermittent fever; it was also used as anthelmintic; but its internal administration was soon considered too dangerous. It was employed in surgery by Cheron, 1876.

Application.—Trinitrophenol is used on burns and the like as a saturated aqueous solution, whose antiseptic efficiency is about seven times that of 1 per cent phenol. It is prepared by dissolving 6 Gm. in a pint of hot water and filtering when cold. Cloths saturated with this solution are applied, covered with dry cotton, and left in place for several days. Stronger alcoholic solutions should not be used. *Picric stains* may be removed from the skin by applying powdered potassium sulfate for a minute, then washing with soap; or by a paste of magnesium carbonate (Mankiewicz, 1916).

The **toxicology** is practically important, especially in munition factories (Alice Hamilton, 1917). The common belief of its use in beers seems to be unfounded (Gadamer). Locally, the handling of the dry powder produces eczematous dermatitis, "picric itch." A measles rash also occurs sometimes in poisoning. Systemically, toxic doses destroy the red corpuscles and produce gastro-enteritis, hemorrhagic nephritis and acute hepatitis. There may thus be a true icterus, although the yellow coloration is mainly due to picric staining (Malmejac, 1917). Industrial exposure to *ammonium picrate dust,* 0.008 mg. per cubic meter, produced no systemic effects, but a tenth of the workers had dermatitis (Sunderman *et al.,* 1945).

Toxic symptoms which arise from its use on burned surfaces include headache, vertigo, nausea, vomiting, diarrhea; erythematous, papular or vesicular rashes; yellow coloration of the skin and conjunctiva; darkened green or port wine-colored urine; albuminuria. These should be checked so that the applications may be promptly discontinued.

The toxic effects on rabbits and dogs are described by Koizumi, 1914; those on frogs by E. D. Brown, Ahlfs and Howard, 1920.

Fate.—A part of the picric acid may be excreted unchanged by the urine, but most is transformed by the liver into picramic acid. This confers the diazo reaction on the urine (Pecker, 1916).

Trinitrophenol, U.S.P. (Picric Acid), $C_6H_2(NO_2)_3OH$, acid to litmus, explosive on percussion, is a yellow crystalline powder, odorless, of bitter taste and intense staining power. Sol. in water (1:80) or alc. (1:12).

TRINITROTOLUENE

This is important as an explosive ("T.N.T."). It is $C_6H_2(NO_2)C_3H_3$. Other nitro and amino derivatives of benzene which are also used as explosives, produce similar effects with differences in detail (Alice Hamilton, 1917). Poisoning arises by inhalation of the dust, in a proportion of the munition workers, generally between the fifth and sixth week of the employment; young and old subjects are more susceptible than vigorous adults (Martland, 1917). It is readily *absorbed* through the respiratory and gastro-intestinal tract, a small amount also through the skin. The *urine* contains dinitroaminotoluene and probably other amino derivatives (von Oettingen *et al.,* 1944; R. K. Snyder, 1946). Slices of muscle and liver convert trinitrotoluene into a compound that inhibits tissue respiration, and then further into a compound that lacks this inhibition (E. Bueding and Joliffe, 1946).

Untoward effects in munitions workers are usually minor: The most frequent is mild *dermatosis* of the hands. The skin of the hands is stained a light yellow, the hair reddish (L. Schwartz, 1944); there is irritation of the respiratory mucosae, sneezing, sore throat and irritant cough. Systemic effects begin with gastro-intestinal irritation, distress, nausea, anoxia, vomiting and diarrhea. The most serious but infrequent complication is *hepatic necrosis* (Livingstone *et al.,* 1916). It occurs even with good working conditions (W. L. Palmer *et al.,* 1943) in about 0.2 per cent of munitions workers, but a fourth to a third of the cases are fatal (von Oettingen *et al.,* 1944). Its infrequency indicates that it requires special susceptibility, probably by *sensitization,* as it occurs only after some months of exposure; but the actual onset is usually sudden. None has been reported after six months of exposure (J. H. Eddy, 1944). *Other occasional clinical effects* include blood destruction, aplastic anemia and purpura (Panton, 1917; B. Moore, 1917); cyanosis of the lips and ears; a deep blue alveolar line (L. Schwartz, 1939); leukocytosis or leukopenia; central nervous changes of varying degree, probably resulting from anoxia; peripheral neuritis and muscle pains which may be early symptoms; cardiac muscular and menstrual irregularities, urinary and renal irritation (von Oettingen *et al.*, 1944). R. F. Sievers *et al.*, 1946, report three cases of aplastic anemia, two with fatal outcome, after exposure to TNT. Necropsy showed hypoplastic bone marrow and subacute atrophy of the liver.

Toxic Effects on Animals.—Dogs and cats are more susceptible to trinitrotoluene than are rabbits and guinea pigs (C. Voegtlin *et al.*, 1921). Administration to dogs over several months produced irritation of the digestive tract and urinary bladder; ataxia, nystagmus, circus movements; and moderate anemia (von Oettingen *et al.*, 1944). The chief pathologic finding in various animals is general hemosiderosis; sometimes moderate fatty degeneration of the liver and perhaps of the kidneys, attributable to methemoglobinemia (R. D. Lillie, 1943). M. I. Smith *et al.*, 1943, found no changes in the glycuronic acid excretion; porphyrin may be somewhat increased. H. J. Channon *et al.*, 1944, studied the *fate* of TNT in rabbits.

Effects of Diet.—H. P. Himsworth and Glynn, 1942, reported that the chronic toxic effects for rats are greater on a diet rich in fat, and are decreased by high protein or carbohydrate feeding. Addition of milk to a well balanced diet had no effect on the toxicity; nor did the addition of ascorbic acid; although scorbutogenic diet increases the susceptibility in guinea pigs. Ascorbic acid is slightly protective with cats (M. I. Smith *et al.*, 1943).

Treatment.—Little can probably be done for the fully developed disease, but administration of methionine, 3 to 5 Gm. daily, appears to reduce the mortality (J. H. Eddy, 1945). The workers should be withdrawn from exposure with the first appearance of any symptoms. *Protection* offers the only satisfactory solution of the problem. It involves proper ventilation, cleanliness, and so forth. The subject is discusesd by Schereschewsky, 1917.

Tetryl, trinitrophenylmethylnitramine, used extensively as "sensitive" explosive, produces *dermatitis* in nearly half of the workers, generally after about three weeks of exposure, but most of those affected become "hardened". The palms and fingers stain yellow, the hair red (L. Schwartz, 1944). The dermatitis involves especially the face around the eyes, with erythemia and edema similar to that from second degree burns. The nasal mucosa is also affected, with epistaxis from small ulcerating points. *Systemic effects*, rather rapidly developing secondary anemia, irritability, anorexia, are less frequent. Renal and hepatic damage have not been demonstrated. *Prophylaxis* consists chiefly in control of dust. Protective casein hand creams reduce the incidence to half. Severely affected workers should be eliminated; lighter cases may try to develop tolerance (L. J. Witkowski *et al.*, 1942). *Synthetic antigens*, sensitizing guinea pigs to skin tests, have been prepared from tetryl and related compounds *in vitro* by coupling them to serum proteins (G. P. H. Gell, 1944).

Hexite, hexanitrodiphenylamine, produces vesicular dermatitis in munition workers. Its systemic effects resemble those of nitroglycerin (L. Schwartz, 1944).

COAL TAR DYES

The quality of dyeing generally implies that the dye has a high adsorption affinity, *i. e.*, that it accumulates in high concentration on the surfaces. This increases the concentration in contact with the cell, and modifies its surface properties, and indeed those of intra- and extracellular colloids, similarly to the albumoses, saponins, and the like. The actions of the dyes therefore have similarities independent of their chemical composition. They generally have rather high antiseptic value, often with specific differences that go parallel with the staining action. Protozoa are generally more susceptible than bacteria. Intravenous injection produces acute anaphylactoid phenomena, which have been employed similarly to the foreign protein injections against septicemias, and so on (Churchman, 1925). The injected dye often gives selected concentration in inflamed and injured tissues; for instance, in necrotic tuberculous and cancerous areas (Cecil and Weil, 1917). The excretion is also generally rather selective, either by the urine or more often by the bile (Salant and Bengis, 1916). The rate of the excretion is utilized for studying the functional efficiency of the kidneys and liver. Colloidal dyes leave the blood plasma so slowly that they can be used to estimate the volume of the circulating blood. The greater number of the medicinal dyes belong to a few chemical types. Commercial dyes are often impure and indefinite mixtures.

Intravenous Injections of Colloidoclastic Antiseptics.—Improvement of staphylococcus, gonococcus and other infections may occur after the intravenous injection of antiseptic dyes, arsphenamine, mercurochrome, mercuric chloride, formaldehyde and a number of other antiseptics (H. H. Young *et al.*, 1924; J. S. Simmons, 1929). Directly bactericidal concentrations in the blood would be fatal; but all these agents tend to alter the colloidal equilibrium of the blood, and therefore produce more or less allergic reaction, which may be responsible for the improvement, but also implies an element of danger.

The *penetration of dyes into cells* presents interesting problems (A. P. Mathews, 1910). Basic dyes diminish, acid dyes increase the imbibition of gelatin. This may be a factor in the penetration, but is not a complete explanation (Traube and Koehler, 1915). The vital staining and the toxicity of acid and basic dyes are not parallel (Hoeber, 1914). The addition of dyes to other poisons often modifies their toxicity (Sellei, 1913).

Yeast.—Basic dyes (methylene blue) stimulate yeast growth in dilute solutions and inhibit with moderate concentrations. Acid dyes have little effect (Somogyi, 1916). There is no correlation between the effects on yeast and excised frog heart or mammalian intestine. (Axmacher, 1933).

Tissue Cultures.—The growth of cultures from embryonal chick lung is accelerated by weak solutions of various dyes, and inhibited by stronger concentrations (Kamon, 1928).

Effects of Dyes on Cancer.—Selective staining of cancers by dyes does not imply selective toxicity; it is generally due to the presence of necrotic tissue. Indeed, injection of trypan blue (or colloidal metals) increases the susceptibility of mice to transplantation carcinomas (Ludford, 1932). Zahl and Waters, 1941, suggested the possibility of using the localization of Evans blue or lithium carmine in the semi-necrotic zone of tumors for introducing radioactive substances.

METHYLTHIONINE CHLORIDE, METHYLENE BLUE

This dye (tetramethyl thionine chloride) and its colorless reduction derivatives furnish an oxidation-reduction system with interesting reactions in the test tube and in organ emulsions, resembling somewhat those of the cellular respiration ferments. It has been suggested that it may substitute for these, but this is doubtful for intact animals. It forms methemoglobin, on intravenous injection as well as in shed blood, the latter with hemolysis; this is probably the explanation of its antidotal action in cyanide poisoning. It penetrates cells fairly readily and is used for intravital staining of nerve tissue. It has a variety of actions, but its therapeutic applications have generally turned out inferior to other agents. It was tried as an analgetic in neuralgia and neuritis, as an antipyretic and parasiticide in malaria, and as an antiseptic in cystitis, urethritis, conjunctivitis and skin diseases. It colors the urine green or blue and may be used as a kidney function test (Tachau, 1911).

Fate.—Methylene blue is distributed through all tissues (localization in kidneys, G. D. Shafer, 1908), but it is rapidly reduced to colorless leuko compounds. These are oxidized when the tissues are exposed to air (Herter, 1904), or are in contact with hydrogen peroxide, thus restoring the blue color. Prolonged ingestion (as analgetic) gives a blue tint to the vitreous humor; this is the only tissue in the body which is blue before exposure to the air.

Excretion occurs by the urine and feces (traces in the sweat and sputum), partly unchanged and partly as "methylene azure." The latter is also present in medicinal methylene blue, being formed from it by alkalis. Both exist in a colored and colorless (reduced) form in the urine (Underhill and Closson, 1905). This is therefore rendered more blue by oxidizing agents, especially in acid reaction, and paler by reducing agents (dextrose, and so forth).

Test of Kidney Function.—After hypodermic injection of 0.02 to 0.5 Gm. the excretion begins normally between fifteen to twenty-five minutes later. The usefulness of the test is more limited than that of the phenolsulfonphthalein test.

Urinary Antisepsis.—Methylene blue (1:150,000) is antiseptic for pure cultures; but it is a slow and weak germicide and practically inactive in the leuko form, in which it is excreted in the urine. In doses of 0.4 to 0.6 Gm., four times daily for several days, it perhaps is of some use in staphylococcus cystitis, but useless in urethritis (Hinman, 1915).

Methylene Blue Oxidation-Reduction Reactions.—The dye is readily reduced to a series of colorless (leuko) compounds (four have been demonstrated in the urine), and these may be reoxidized to the blue dye. Through these reactions it acts as an oxidizing and reducing "carrier" in some rather peculiar reactions, probably through its sulfhydryl group, and it may to some extent take the place of glutathione (review, Harrop and Barron, 1928).

The oxidative effects (with decolorization of the blue) include the incomplete oxidation of glucose (Warburg), and the oxidation of hemoglobin to methemoglobin. *As a reducing agent* it prevents the oxidative effects of blood charcoal (Warburg) and the spontaneous oxidation of ethers. It checks the oxidation of succinic acid by hashed muscle (Battelli and Stern). In this it inhibits not the dehydrogenation but the oxidation of the hydrogen (Thunberg). It greatly increases the respiration of mammalian erythrocytes, and Meyerhof believed that it increases tissue respiration; but the evidence for its action on living cells is not satisfactory.

Its use in carbon monoxide poisoning was based on a theory that it would take the place of hemoglobin as a conveyor of oxygen to the tissues. It appears to be not only useless, but toxic, for it augments the phenomena of anoxia in animals (Crisler, 1935). It is reported to improve efficiency of performance at *high altitudes*, if 0.2 to 0.04 Gm. is administered about two hours before the ascent (M. M. Brooks, 1945).

Actions on Hemoglobin.—Methylene blue can oxidize hemoglobin to methemoglobin or again (in its leuko form) reduce methemoglobin to hemoglobin, according to circumstances. In severe methemoglobinemia, from nitrite, acetanilide or sulfanilamide, in man or animals, intravenous injection of small doses of methylene blue (1 to 2 mg. per Kg.) promptly decreases the methemoglobin and increases the oxygen capacity of the blood, or it may be administered orally, 65 to 130 mg. every four hours, for man (W. B. Wendel, 1938; A. F. Hartmann *et al.*, 1938; A. P. Richardson, 1939; D. Campbell and Morgan, 1939). On the other hand, methylene blue injection is effective in cyanide poisoning (although not so effective as nitrite) by forming methemoglobin to bind the cyanide. Methylene blue is also *hemolytic.*

Experimental Tumors.—The injection of methylene blue into rat and mouse tumors increases the number of egressions from 3-8 per cent to 25-44 per cent. Other dryes are ineffective (M. M. Brooks, 1934).

Malaria.—Methylene blue, 0.1 to 0.15 Gm., is recommended by Froes, 1934, as adjunct to quinine or atabrine (in their usual dosage).

Leprosy.—Rozental, 1935, claimed diminution of the bacteria and marked clinical improvement from the intravenous injection of aniline dyes that have selective affinity for the leprous lesions: 1 per cent methylene blue or 0.5 per cent of "brilliant green," 5 to 30 cc. every five to six days for several months.

Tsutsugamushi infections of mice are reported to respond remarkably well to treatment with methylthionine chloride (W. F. McLimans, 1947).

Toxic Actions.—Therapeutic doses sometimes cause slight vesical or gastro-intestinal irritation. Hypodermically, it may produce ulcers and abscesses. Its toxicity is low, the fatal dose for dogs exceeding 1 Gm. per kilogram. Intravenously, 0.5 Gm. per kilogram kills by respiratory paralysis; considerably smaller doses may produce marked circulatory disturbances. Its continued oral use is harmless (Tanfiljeff, 1907). Rats tolerate 500 mg. per Kg. as 5 per cent solution by mouth, or 150 mg. per Kg. as 1 per cent solution hypodermically, but are killed by 200 mg. per Kg. hypodermically, and by 50 to 100 mg. per Kg. intraperitoneally (H. H. Anderson *et al.*, 1934).

Peripheral Autonomic Actions.—In general, small concentrations of methylene blue produce parasympathetic stimulation, perhaps by inhibiting cholinesterase. Moderate concentrations paralyze the parasympathetic receptive mechanism, similarly to atropine (R. P. Cook, 1926).

Blood Pressure and Respiration.—Intravenous injection of 4 mg. per Kg. produces marked rise of blood pressure, followed by fall (Garfounkel and Gautrelet, 1913) by direct action on the vessels (Addarii and Freundlich, 1937). Perfused blood vessels are first constricted and then dilated. The *respiration* is stimulated by small and arrested by large doses (Lundberg). It shortens the time when exposure to oxygen results in pulmonary edema (Gregoire, 1931). The *heart rate* is slowed by intravenous injection and by perfusion of the excised heart with dilute solutions of methylene blue (Lundberg, 1924). On the other hand, it is antagonistic to drugs that stimulate the vagus, although it is less potent than atropine (C. Heymans, 1922). This is a reversible effect on the cell surface, before the protoplasm is stained (R. P. Cook, 1926). Methylene blue also inhibits the *cholinesterase* of the serum, in low concentration, but much less effectively *in vivo* (E. Rentz, 1940). The excised frog's heart is stimulated by small doses; large doses destroy its irritability.

Hyperthermia.—Moderate doses raise the temperature, as was first shown by Ehrlich. The action is central, and results in increase of gaseous metabolism and decrease of liver glycogen. With rats, these effects do not occur if the environmental temperature is below 24° C. (Gregoire, 1931).

Intestine is stimulated by 1:10^6; with 1:10^4 this is followed by inhibition. Atropine antagonizes the stimulation only imperfectly (Lundberg).

Uterus is also stimulated, irrespective of its response to epinephrine. It can then be inhibited by large doses of atropine, but not by ergotoxine (Lundberg). High concentrations are depressant (R. P. Cook, 1926).

Somnifacient Adjuvant.—Konzett, 1938, reported that pretreatment of rats and other animals with small intraperitoneal doses of methylene blue or other liposoluble dyes (neutral red, and so forth) considerably strengthens the action of soporifics (chloral, phenobarbital, and the like). The dyes alone are not somnifacient even in larger doses. Congo red, which is not liposoluble, is ineffective. Intravenous injection of methylene blue intensifies the *electrical activity of the cerebral cortex* (Moruzzi, 1938).

Preparation.—*Methylene Blue,* U.S.P.; *Methylthionine Chloride,* (not to be confused with *methyl blue*), occurs as dark green crystals; freely soluble in water (1:25) and alcohol. Dose, 0.06 to 0.3 Gm., 1 to 5 grains; externally, 0.5 per cent solution on mucous membranes, 2 per cent on skin.

PHENOTHIAZINE (THIODIPHENYLAMINE)

This substance, prepared by the action of sulfur on diphenylamine, is an effective *insecticide,* in concentrations which are not toxic for higher animals and man. It is more toxic than rotenone to mosquito larvae (F. L. Campbell *et al.*, 1934). It is also an effective *anthelmintic* against oxyuris (1 to 4 Gm. per day, according to age, for five successive days, N. Sisk, 1943), but it sometimes produces *anemia* and *toxic hepatitis* (D. Hubble, 1941). It gives rise to local irritations of the *skin,* and its oxidation products sensitize the skin to irritation by light (also with pigs; Swales *et al.*, 1942).

Properties.—Phenothiazine is a pale yellow crystalline powder, practically tasteless, soluble in fat solvents and in alcohol, practically insoluble in water, oxidizing slowly in moist air. It is the parent substance of many "thiazine" dyes, especially thionol, Lauth's violet and methylene blue.

Fate.—Phenothiazine is rapidly excreted by the urine, partly as such and partly as the more soluble oxidation product thionol, a red dye related to methylene blue. In acid urine this is reduced to leukothionol, which is bactericidal in both acid and alkaline reaction (below *p*H 4.5 and above 8), but not in neutral solutions (De Eds, Eddy and Thomas, 1938; J. O. Thomas *et al.*, 1938). Rabbits excrete about 50 per cent in the urine as colorless conjugate (G. H. Benham, 1945). Leukothionol is oxidized to thionol when exposed to sunlight under anaerobic conditions (De Eds, Wilson and Thomas, 1940).

Urinary Tract Infections.—Good results are reported with daily doses of 1.3 to 2 Gm. by mouth, the total course not to exceed 15 Gm., when it should be intermitted. The urine should be kept at *p*H 4.5 to 5.5 by ammonium chloride, With this dosage no untoward effects were observed; but long continuation of excessive doses may produce secondary *anemia,* apparently hemolytic, similarly to methylene blue (De Eds, Stockton and Thomas, 1939). It accelerates saponin hemolysis of horse erythrocytes *in vitro,* but does not produce photodynamic hemolysis (H. B. Collier and Allen, 1942).

TRIPHENYLAMINE (ROSANILINE) DYES

The basic dyes of this group, especially *gentian violet, crystal violet* and *methyl violet,* have a selective toxicity for gram-positive bacteria, especially staphylococcus, B. pyocyaneus and B. diphtheriae; and a much weaker action on the gram-negative species. They have a low toxicity for tissues, and penetrate them readily. The acid dyes (acid *fuchsin*) act selectively on gram-negative organisms.

Composition.—These dyes are derived from triphenyl methane, $H.C:(C_6H_5)_3$. *Pararosaniline* is triamine-triphenyl-carbinol, $(C_6H_4NH_2)_3COH$, and *rosaniline* is triamino-diphenyltolyl-carbinol, $(C_6H_4NH_2)_2(C_6H_3.CH_3.NH_2)COH$. *Fuchsine* (magenta, aniline red) is a mixture of rosaniline and pararosaniline chloride. *Basic fuchsine* is a corresponding acetate; and *Acid fuchsine* (ruby S) is the acid sodium salt of fuchsine disulfonic and trisulfonic acds. The introduction of methyl groups into para-, rosaniline-fuchsine results in a series of violet dyes grouped in the U.S.P. as *Methylrosaniline Chloride: gentian violet* is a mixture of penta- and hexa-methyl pararosaniline chloride; *methyl violet* consists mostly of the pentamethyl, and *crystal violet* of the hexa-derivative. Crystal violet is most readily obtained in pure form; but so far gentian violet has been most extensively used. In fact, many of the statements refer to dyes that had been diluted with indefinite quantities of dextrin. *Brilliant green* (malachite green) also belongs to the triphenylamine group.

Gentian Violet.—The selective action on *bacteria* was investigated especially by Churchman, 1914. Its relative harmlessness to tissues is illustrated by the observations of Russel, 1914, that tissue cultures are not injured by the concentrations which kill bacteria. The oral minimal fatal dose for rabbits is 22 mg. per Kg. daily for six days. Dogs are more tolerant (W. H. Wright and Brady, 1940).

Local Application.—Gentian violet is a rather good superficial antiseptic for wounds, burns, ulcers and inflamed mucous membranes. It is applied as $\frac{1}{10}$ to 1 per cent solution. The latter, used on burns as a spray or in tragacanth jelly, forms a tough, pliable film and eschar, which is less subject to infection than is the tannic acid eschar, though it has similar limitations (R. H. Aldrich, 1933; J. H. Cornell *et al.*, 1933; R. D. McClure, 1939). Devine, 1939, treats burns with a three-dye solution, 1 per cent of gentian violet and brilliant green, and 0.1 per cent of neutral acriflavine. This keeps indefinitely and is applied with a swab, without scrubbing or dressing. The staining is the chief objection.

Oral Use.—Gentian violet has been used in *colitis*, 0.065 Gm., 1 grain, three times daily, in capsules. It is an effective *anthelmintic*. For *oxyuris*, W. H. Wright and Brady, 1940, found it superior to all other treatments. The dosage for adults is two tablets of 30 mg., $\frac{1}{2}$ grain, three times daily, before meals. They may be enteric coated. Some patients react with nausea, vomiting and diarrhea, but these subside quickly if the dosage is reduced or temporarily discontinued. *Contraindications* are ascaris, and fairly severe cardiac, hepatic, renal or gastro-intestinal disease, and alcohol. Gentian violet is also effective against *Strongyloides stercoralis, Clonorchis sinensis* and other liver flukes. It is administered as enteric-coated tablets of 0.06 Gm., three times daily immediately after meals, for one or two weeks. It is usually well tolerated, but some patients have temporary intestinal discomfort and nausea (E. C. Faust, 1926, 1937).

Intravenous Injection.—Young and Hill, 1924, claimed good results in septicemia, in chronic cystitis and in osteomyelitis, when caused by staphylococcus. They inject 5 mg. per Kg. of the body weight, as 0.5 per cent dilution, repeated in five hours if necessary. The skin immediately takes a markedly blue tint from the dye, which disappears in a few hours. It has been shown on animals that the intravenous injection of gentian violet produces marked but brief fall of blood pressure, which may be preceded by a sharp rise. These effects occur also after pithing, so that they are peripheral (presumably of the allergic type). The respiration is not affected (Pindar and Donnelly, 1925).

Methylrosaniline Chloride, U.S.P. (*Gentian,* Methyl or Crystal Violet), is a mixture of hexa, penta and tetramethyl pararosaniline chlorides. It occurs as a dark green powder or pieces, with metallic luster. Soluble in 40 parts of water and in 10 parts of alcohol, insoluble in ether. Dose, 60 mg., $\frac{1}{2}$ grain, in enteric-coated tablets.

Brilliant Green (*Malachite Green*).—Leitch, 1917, claimed high antiseptic power and satisfactory results in wounds.

Acid Fuchsine.—Churchman found that this kills gram-negative organisms (Bacillus prodigiosus) in concentrations that had no effect on the gram-positive (B. anthracis); but this selective action occurred only at a temperature (50° C.) materially above that of the body.

Basic Fuchsine (Gruebler), pararosaniline acetate, was advised by May, 1912, and Donnelly, 1914, as a lotion or ointment (1 per cent) for ulcers and burns. It is antiseptic, nonirritant, nontoxic and seems to encourage epithelial growth and granulation. The color may be removed from the skin by alcohol.

AZO DYES

Azo- and diazo-compounds, derived from $C_6H_5.N=N.C_6H_5$ and $C_6H_5\text{—}\underset{\substack{|\\ Cl}}{N}\equiv N$, are important intermediates of many dyes and organic chemicals.

Congo red (diphenyl p-o-bis sodium azonaphthionate) is a colloidal dye with detoxicant actions, perhaps due to adsorption of the toxic substances. It also produces peculiar effects on blood coagulation and formation. Because of its slow diffusion, it may be used to estimate the blood plasma volume. Different samples vary materially in colloidal properties.

Toxicity and Systemic Effects.—With intravenous injection of 1 per cent solution of congo red 4 B (Coleman and Bell), dissolved in 5 per cent dextrose, which gives a more stable solution than sodium chloride, the LD_{60} for various mammals and for pigeons ranges from 150 to 250 mg. per Kg. The toxic symptoms consist in general depression and collapse; death occurs by circulatory collapse, the result of cardiac depression. Perfused hearts react with increased tonus and systolic arrest. Smooth muscle of the bladder, uterus and intestines is stimulated. Their reaction to autonomic drugs is not altered (A. P. Richardson and Dillon, 1939).

Detoxicant Actions.—Ishigami, 1928, found that congo red and other colloidal dyes which have practically no effect on gastrocnemius preparations when used alone, weaken materially the action of curare and guanidine, not that of nicotine, very slightly that of oxalate. They do not affect the actions of pilocarpine, epinephrine, cocaine and strophanthin on the excised frog heart or excised rabbit intestine. These results were confirmed and extended by Thienes, 1930: Injection of congo red into frogs several hours before or simultaneously with the poison antagonizes the "curare action" of curare, tetramethylammonium, sparteine and brucine, and the spinal convulsant actions of strychnine and brucine. The dye is generally ineffective if injected after the onset of the symptoms. It does not affect the action of atropine on the vagus. It also inhibits the convulsions of descending galvanic currents; but it has no effect on the narcosis of ascending galvanic currents, nor does it enhance the paralyzant action of other drugs, nor is it in itself paralyzant. Methylene blue and neutral red, on the other hand, are directly depressant (Köllensperger, 1938).

Brilliant vital red has been used as *anticonvulsant in epilepsy,* with variable success. A 1 per cent solution is injected intravenously, at first 10 to 15 cc., then 30 cc., daily, with omission every third or fourth day to avoid renal irritation (S. Cobb, Cohen and Ney, 1938; R. Osgood and Robinson, 1938).

Antihemolytic Action.—The addition of 0.1 per cent of congo red protects human corpuscles against hemolysis by hypotonic saline, hypertonic urea in saline, bile salts and saponin. This is attributed to the formation of a film of congo red on the cells. It increases hemolysis by hypotonic dextrose solutions, ether and urea in water (A. P. Richardson, 1939).

Blood coagulation is affected by several colloidal dyes, being generally hastened by small doses, and delayed by large doses. With intravenous injection of *congo red* (as 1 per cent solution) into rabbits, Taliaferro and Haag, 1937, found that 10 to 20 mg. per Kg. diminishes the coagulation time, while this is greatly increased by 200 mg. or more; the M.L.D. being 300 mg. per Kg. Coagulation is also delayed by adding it in the test tube. In dogs, 5 to 25 mg. per Kg. does not shorten the coagulation time, but rather delays clotting time (Richardson, 1939). In man, it is shortened by 10 to 15 cc. of 1 per cent, by vein. This dosage repeated daily as needed was recommended by Wedekind *et al.*, 1930, as clinically *hemostatic* in various persistent hemorrhages involving diminished blood coagulation. Acute traumatic hemorrhage is not affected, nor is oral or hypodermic administration effective. The mechanism of the hemostatic action is not understood; but it is accompanied by increase of fibrinogen, platelets and monocytes (Nikolajew and Gusewitch, 1935). Daily intraperitoneal injections for three to eight days raise the plasma prothrombin (W. A. Barnes, 1942). It does not occur in rabbits (Richardson, 1939). *Chlorazol Sky Blue* F F (Chicago Blue) prevents clotting by inhibiting the effect of calcium and thrombokinase on the fibrinogen-prothrombase complex (Huggett and Silman, 1932). *Chlorazol fast pink* B K S is injected in physiological experimentation to check blood coagulation (Modell, 1939). It is more effective than heparin (Huggett and Rowe, 1932).

Reticulocytes.—Intravenous injection of congo red into patients with pernicious anemia, or into guinea pigs, evokes a shower of reticulocytes. The effects of repeated injections may resemble those from liver extract, but they often fail. The clinical dosage is stated as 10 cc. of 1.5 per cent "congo red 4 B" in 6 per cent dextrose, daily for five to ten days (Mermod and Dock, 1935; Massa and Zolezzi, 1935).

Fate.—Congo red practically disappears from the blood within twenty-four hours after intravenous injection. It is distributed chiefly to the organs that contain large amounts of extracellular fluid. The kidneys retain a rather high concentration. The excretion occurs chiefly by the bile (Richardson, 1939).

Dye Method of Determining Plasma Volume.—The dyes that have been used for this purpose include congo red, vital red, trypan red, blue azo dyes and numerous others (Dawson, Evans and Whipple, 1920). "*Water blue,*" a nontoxic triphenylmethane dye, is especially slow to leave the blood stream (Hemingway *et al.*, 1935). The rate of disappearance of congo red from the blood is utilized diagnostically. It is slowed by impaired liver function (Ninomiya, 1928) and quickened in amyloid disease—the latter because congo red is selectively absorbed by amyloid (E. Wallace, 1932). *Evans blue* (Dye T-1824) is fatal to cats and dogs if 10 cc. per Kg. of 0.5 per cent solution are injected intravenously; delayed death may occur with 3 to 5 cc. (Hueper and Ichniowski, 1944).

Toluidine blue, alizarine blue S and indigo carmine increase the *oxygen uptake* by slices of rat kidney, and partially counteract cyanide (Axmacher, 1935).

Indigocarmine is used for coloring Mercuric Chloride Poison Tablets, and also as a kidney function test. It occurs as a blue powder or paste, sparingly sol. in water; insol. in alc. Dose, subcutaneous or intramuscular injection, 0.05 to 0.1 Gm., ¾ to 1½ grains; intravenous injection, 0.008 to 0.016 Gm., ⅛ to ¼ grain, B.P.

"Scarlet red" is a rather complex toluylnaphthol derivative with two azo links. It is used as 4 to 8 per cent ointment, to stimulate the growth of epithelium on clean granulating wounds, especially on burns and on clean ulcers (Schmieden, 1908; Morawitz, 1909). It may also be employed as solution in oil and as dusting powder (diluted with talcum). Its application should be confined to the areas of active epithelial proliferation. The 8 per cent ointment often produces irritation and even erosion and should therefore be alternated with a soothing ointment. Systemic effects (violent gastro-enteritis, Lyle, 1912) have been reported. Although scarlet red has been in use for many years, clinical opinions as to its value are still divided. It is conceded to be ineffective in chronic ulcers, if the local circulation is impaired. O. Sachs, 1911, claims that a number of other aniline dyes also stimulate epithelial growth, but the property is especially prominent in the compounds allied to amido-azo-benzene (Martinotti, 1914).

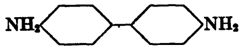
In *cancer,* the necrotic areas accumulate diazo dyes, but no therapeutic effects have been attained (R. Weil, 1916). The toxicity of diazo dyes was studied by Cecil and Weil, 1917.

Orthotoluene-azobetanaphthol is used as an oil-soluble dye for citrus fruit. Climenko, 1937, found 1 to 5 mg. in the peel of dyed fruit, none in the pulp or juice. Its toxicity for animals is low, acutely or chronic.

Pyridium, an azo dye (phenyl-2-6-diamino-pyridine monohydrochloride), was introduced as an oral urinary antiseptic (0.2 Gm. in capsules, three times daily), but it was found to be practically ineffective (Report, with bibliography, Council on Pharmacy and Chemistry, J.A.M.A., 1933, *101:* 2118). With clinical administration of 0.6 Gm. per day, an eighth to half is *excreted* by the urine, and this becomes somewhat bacteriostatic against Staphylococcus aureus and against coli (Goerner and Haley, 1932). Rapid intravenous injection of pyridium causes transitory fall of blood pressure. Massive oral doses form methemoglobin. Prolonged oral administration to dogs produces liver damage and erythropenia (Walton and Lawson, 1934).

BENZIDINE DYES

Trypan red and **trypan blue** are complex derivatives of benzidine (paradiamino diphenyl),



Ehrlich found that these have a high toxicity for trypanosomes. Repeated small injections of trypan blue into mice result in mitosis of the liver cells, with reduction of glycogen storage (H. W. Deane, 1944).

Suramin Sodium (*naphuride sodium Germanin,* "Bayer 205," moranyl, naganol, antrypol), the sodium salt of a complex aromatic aminosulfonic acid carbamide, was introduced as *trypanocide* in African "sleeping sickness" from T. gambiense infections. It is highly successful clinically, producing a temporary "clinical cure," even in advanced cases, but with later relapse. It is *excreted* very slowly and meanwhile gives protection against infection for several months, making it especially effective for prophylaxis. The slow excretion also tends to cumulative action, and its concentration in the blood and cerebrospinal fluid should be controlled by the Wormall test, as a routine of treatment (F. Hawkin, 1940).

It is also used in *pemphigus,* with varying results (Wells, Humphrey and Wells, 1937).

Its *toxicity* is relatively low, but it has a tendency to produce renal irritation, with casts and albuminuria, lasting some six weeks and generally disappearing spontaneously. Hemolysis, dermatitis and fever occur occasionally, agranulocytosis rarely. A few fatalities have been erported. Toxic doses of suramin sodium produce intense zonal degeneration of the adrenal cortex in guinea pigs, and there are indications that this may occur clinically (E. M. Humphreys and Donaldson, 1941). *In animals,* the most striking phenomenon is the duration of the effect: a single injection not only frees the blood from trypanosomes, but renders the animal resistant to infection for days to months, and during this period the serum is curative when injected into other animals. The substance itself, however, has little effect on the parasites *in vitro;* in animals, also, the action is delayed for several days; and the therapeutic response is greatly influenced by the species of the infected animal. It appears therefore that some complex cooperation of the host is involved in the production of the parasiticidal substance. This is not an ordinary immune substance, for this activity is not destroyed by heating. *Plasma globulin* and probably other proteins combine with germanin, perhaps by adsorption. This causes prolonged retention of the substance in the plasma and tissues (Boursnell and Wormall, 1939). The serum proteins undergo a marked change on the addition of germanin (2 per cent); they become incoagulable by tannic acid, metallic salts or heating to 60° C. (Kocian, 1936; references, Dale, 1923); and fail to provoke anaphylactic shock in sensitized animals (Makarowa and Zeiss, 1923), owing to denaturation (Steppuhn *et al.,* 1923) in which the sulfonic group is probably involved (Roehl, 1926). It tends to prevent flocculation of congo red, mastic and benzoin by electrocytes (O. Jirovec, 1943). It forms complex compounds with *calcium* and thereby decreases the calcium ion concentration in solution (Mulli *et al.,* 1933). This may be concerned in its inhibiting effect on blood coagulation.

Suramin Sodium, U.S.P., *naphuride sodium,* is a white, odorless, slightly bitter powder, readily soluble in water, forming a neutral solution. It is administered *intravenously* as a freshly prepared solution, made by sprinkling the powder on the surface of water, to prevent lumping. The initial *dose* for treatment of trypanosomes or pemphigus is 0.3 to 0.5 Gm. in 10 cc. of water, followed by 1 Gm. in 10 cc. every four days until 10 Gm. have been administered. Caution should be used if renal irritation develops. The course should not be repeated until four months have elapsed. The prophylactic dose for protection against trypansomiasis is 1 Gm. every two or three months.

Diamidino Stilbene is reported highly effective in Indian Kala Azar, with 98 per cent of immediate cures and few relapses. However, it is often followed by serious toxic reactions, paresthesia and partial anesthesia of the trigeminal area, with degenerative lesions in the principal sensory pontine nucleus of the trigeminal nerve, developing sometimes months after the administration (S. Gupta, 1943).

Pentamidine (4.4′-diamidino diphenoxypentane) is used against trypanosomes. A death has been reported, following three doses of 0.1 Gm. (McComas and Martin, 1944).

PHTHALEIN DYES

Phthalic anhydride furnishes two series of dyes of medical interest, (1) the phenolphthaleins and (2) the resorcinolphthaleins or fluoresceins.

Fluoresceins.—Sodium fluorescein (*uranin*) retains its color in extremely dilute solutions and has an intense fluorescence: this is true also of the tetrabromine compound, *eosin,* and of the tetraiodine compound, *erythrosin.* Fluorescein is used locally for revealing abrasions and foreign bodies on the cornea and conjunctiva; and by oral administration to test the permeability of the ocular vessels, in the diagnosis of intra-ocular inflammation; and as a renal function test. It is also used to tint solutions, for instance, of local anesthetics; and to trace water supplies. Its toxicity is low; but the fluorescence of eosin and erythrosin sensitizes to the longer light rays, which are irritant and destructive to protoplasm.

Eosin and Erythrosin.—Rost, 1915, found the oral administration of eosin harmless in man and animals. On intravenous injection, the toxic effects of eosin and erythrosin are much higher than those of fluorescein (Salant and Bengis, 1917). Hypersusceptibility to tetrabromfluorescein in lipsticks has resulted in contact dermatitis and gastro-intestinal irritation (R. Hecht *et al.*, 1939).

Diagnosis of Corneal Injury.—Two per cent of fluorescein is dissolved in water by the aid of 3 per cent of sodium bicarbonate. When dropped on the eye, this does not stain the tissue protected by living epithelium; but where this has been injured by abrasions or ulcers, the dye penetrates and produces a green stain. Foreign bodies appear surrounded by a green ring. Loss of substance in the conjunctiva leads to a yellow stain. These phenomena were discovered by Ehrlich, 1882, and introduced into practice.

Diagnosis of Intra-Ocular Inflammation.—When fluorescein is administered by mouth, the whole body takes on a jaundice color, which appears in twenty-four hours. Here also the normal eye is not colored, the dye being retained in the posterior chamber; but in the presence of intra-ocular disease, glaucoma, iritis, and the like, the aqueous humor is colored bright green in about twenty minutes, thus differentiating these diseases from conjunctivitis, in which there is no coloration. The dose by mouth for adults is 3 to 6 Gm.; for children, 1.5 to 2 Gm., in water. This presents no danger (Hamburger, 1909).

Renal Function Test.—This was described by Strauss, 1913. Fluorescein sodium, 1 Gm. in a cup of tea, is given on an empty stomach. Normally, it appears in the urine (best seen when alkaline) in ten to twenty minutes, and lasts thirty-five to forty hours. In renal disease, it appears later and lasts longer. The skin may be stained slightly yellow, but there are no other side effects.

Diagnosis of peripheral vascular disorders is facilitated by long wave ultraviolet illumination after intravenous injection of fluorescein sodium (K. Lange and Boyd, 1944).

Leprosy.—Ryrie, 1936, reported marked improvement with phthalic acid and fluorescein but frequent relapes.

Fluorescein Sodium, U.S.P. (Fluorescein Soluble, Resorcinolphthalein Sodium), is freely sol. in water and in alc. It has strong fluorescence even in extreme solution, but it disappears on acidulation.

Fluorescent Substances and Light.—V. Tappeiner and Rabb (1903) showed that fluorescent substances are destructive to all forms of life and to ferments and toxins, but that the effects appear only in the presence of the specific light rays which induce the fluorescence (review, Tappeiner, 1909; Iodlbauer and Haffner, 1921).

Clinical Manifestations.—Rats or guinea pigs can be photosensitized by intraperitoneal injection of 1 mg. of eosin, or by feeding ripe buckwheat, or an alcoholic extract of the hull, or by the injection of hematoporphyrin, and by other fluorescent substances. Exposure to sunlight causes erythema, pruritus, lacrimation, edema of the face, opacity and ulceration of the cornea, and nervous disturbances (F. P. Mathews, 1938).

Smooth Muscle.—All forms are stimulated by ultraviolet light directly and by strong daylight after sensitization with fluorescent substances (for instance, an hour after the intravenous injection of 6 cc. of 10 per cent eosin into a rabbit). The action appears to be directly on the contractile mechanism. Excessive ultraviolet irradiation injures excised intestinal muscle (Adler, 1920).

If the excised stomach of a frog is treated with a dilute solution of eosin, it goes into tonus when exposed to light, and relaxes in the dark; mammalian intestine is permanently paralyzed (Kolm and Pick, 1920).

Isolated Heart.—When this is sensitized by small doses of eosin or benzoflavin, its tonus is increased by exposure to light, and relaxed by darkness. Larger doses of the sensitizants, or prolonged exposure to light, also depress (Viale, 1923).

Plants.—Eosin and erythrosin are toxic in the light, not in the dark (Shanz, 1923).

Phenolphthalein is discussed under the Cathartics. *Phenolsulfonphthalein,* which is used as a test of renal function, is formed by substituting SO_2 for the CO in phenolphthalein. Delayed and diminished excretion indicates the existence and degree of renal impairment (Abel and Rowntree, 1909; Rowntree and Geraghty, 1910; Chesney, Marshall and Rowntree, 1914). In *Phenoltetrachlorphthalein,* used as a test for hepatic function, the four H atoms in the phthalic ring have been replaced by Cl. These dyes are injected intramuscularly, and their concentration in the excretions is measured colorimetrically, after the addition of alkali which produces a molecular rearrangement that results in the red color. In *Tetrabromphenolphthalein,* two Br atoms are introduced into each phenol ring (not into the phthalic ring, as with the tetrachlor compounds.) The bromine atoms render this compound opaque to roentgen rays; and as it is excreted in the bile, it is used to outline the gallbladder. Details of these tests may be found in N.N.R.

Phenolsulfonphthalein.—In dogs, Arbuthnot *et al.*, 1917, found that with intramuscular injection the urinary excretion varies greatly according to the rate of absorption. With intravenous injection, about 80 per cent is excreted in an hour, regardless of the amount injected (between 3 and 30 mg.). The amount excreted is practically independent of the quantity of urine (beyond a certain minimum). A considerable part is temporarily stored in the tissues before it goes into the urine (Bernheim, 1926). Some is excreted by the bile, and some is lost by reduction, so that the recovery is not quantitative (Kendall, 1917). Suppression of the biliary output by *hepatic injury* increases the total urinary output. *Subdural injections* are normally followed by the appearance of the drug in the urine within ten minutes, but it may be considerably delayed in diseases of the central nervous system, especially when the meninges are involved (Mehrtens and West, 1917) *Other compounds related to phenolsulfonphthalein* are also excreted by the kidneys. These may be somewhat antiseptic (E. J. Davis, 1918).

Phenolsulfonphthalein, U.S.P. (Phenol Red), is slightly sol. in water (1:1300), readily soluble in dilute alkalis. Dose, by intravenous or intramuscular injection, 6 mg., $\frac{1}{10}$ grain. *Phenolsulfonphthalein Injection,* U.S.P., in alkalinized sodium chloride solution; usual size, 6 mg. in 1 cc.

Phenoltetrachlorphthalein Test of Hepatic Function.—The disodium salt is injected intravenously (not intramuscularly or subcutaneously), 5 mg. per Kg., as 2 per cent solution (marketed as ampuls), and its excretion determined either by the quantity in the stools (Rowntree, Hurwitz and Bloomfield, 1913) or by the duodenal tube (Aaron, Beck and Schneider, 1921), or its disappearance from the blood stream (S. M. Rosenthal, 1922). The effect of shock conditions and anaphylactoid drugs on the rates of disappearance of dyes was studied by Hanzlik and De Eds, 1926.

The **tetrabromine** and **tetraiodine** derivatives are discussed under bromine and iodine compounds (see Index).

Dibutylphthalate is used as a plasticizer for cellulose nitrate and acetate lacquers. No toxic effects, external or internal, have been reported, and it is probably harmless. It does not volatilize readily (J.A.M.A., 1934, *103:* 860). **Diallyl phthalate,** used in the manufacture of plastics, produces some local irritation in the workers, and enough may be absorbed from the skin to cause toxic effects (W. A. McOmie, 1946).

Cumarin is directly depressant to the smooth muscle of rabbit uterus and intestine, and to frog heart (Bergstrom, 1928).

ACRIDINE DYES (FLAVINES)

derivative of the coal tar base acridine was introduced by Ehrlich, 1912, as a trypanocide under the name of "trypaflavine." This is now generally called acriflavine and is used as a local and urinary antiseptic, as are also its neutral base and the closely related proflavine.

Acriflavine is diaminomethylacridine chloride hydrochloride; *proflavine* is diaminoacridine sulfate. It differs by the absence of the methyl group. It also is used as *proflavine base.*

Many other acridine dyes have been studied, but are not bactericidal. The preparation and properties of acri- and proflavine were described by Benda, 1912. *Atabrine* is an effective antimalarial agent (see Index); it is an acridine derivative. The *literature,* to 1919, was reviewed by the Council on Pharmacy and Chemistry, J.A.M.A., 1919, *73:* 1542.

Clinical Uses.—*Acriflavine* and *proflavine* are actively antiseptic even in the presence of wound secretions. They are not very toxic to phagocytes and epithelium and therefore interfere relatively little with wound repair (Browning *et al.,* 1919). They are used to check surface infection of wounds and mucous membranes, especially when sulfonamides are contraindicated. Acriflavine is more antiseptic and more toxic than proflavine, but acts more slowly. Neutral acriflavine may be preferred on sensitive mucous membranes where the acidity of the others is objectionable. The flavines seem to have a distinct field for temporarily checking bacterial growth while a wound is awaiting operation; as in transportation with war wounds or in the interval of two stage operations. The best results are obtained by dusting proflavine directly on the wound, and so minimizing its inactivation by absorption into the dressings (G. A. G. Mitchell and Buttle, 1942).

Toxicity.—Tubby *et al.,* 1919, found that rapid intravenous injections kill cats by paralysis of respiration. For rabbits, 10 to 20 mg. of acridine by vein are nonfatal; proflavine is half as toxic. Injurious effects have been reported from industrial exposure to the solid or vapor of acridine, especially violent irritation, burning and itching and sometimes inflammatory swelling of the skin and mucous membranes. It has been regarded as the irritating principle in tar, creosote and pitch that sensitizes the skin to sunlight. The *erythrocytes* show peculiar effects. Proflavine changes their shape to rods in dogs, but not in humans or rabbits. Proflavine and 9-amino acridine powerfully accelerate saponin hemolysis and inhibit lyso-lecithin laking (H. B. Collier, 1945).

Intravenous injection of 2 mg. per Kg. in cats increases the movements of the *uterus* by a direct action on the muscle, enjoining caution against such injections in pregnancy (Sapeika, 1934).

Reinhardt, 1922, claims that *diphtheria toxin* is destroyed by acriflavine, 1:100.

Stains may be removed from the *skin* by soap and water, followed if necessary by 3 per cent HCl in 95 per cent alcohol; or hydrogen peroxide may be added to the soap solution. Linen may be boiled for several hours in a 3.5 per cent solution of sodium perborate.

PREPARATIONS.—*Acriflavine* occurs as a reddish-brown, odorless powder of bitter taste, forming fluorescent solutions in water. These are not injured by boiling, but are sensitive to light. One per cent solutions may be stored in amber bottles for a week. Dilute solutions must be freshly prepared. The flavines are also soluble in alcohol, but insoluble in fat solvents. *Acriflavine Hydrochloride* is freely sol. in water (1:3), insol. in oils.

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MISCELLANEOUS ANTISEPTICS

FORMALDEHYDE

Aldehydes react chemically with a large variety of organic substances, among others with proteins. This probably explains their actions (Liebreich, 1893). Formaldehyde, HCHO, especially is strongly germicidal and is largely used as disinfectant. It hardens the tissues on local contact and thereby produces irritation, especially of mucous membranes. Its systemic toxicity is relatively low. Formaldehyde is a colorless, irritant gas, prepared by the oxidation of methyl alcohol. It is freely soluble in water, and is official in the form of a 40 per cent solution, popularly called *Formalin.* (In making solutions of a given strength, it is necessary to take two and one-half times as much of the commercial solution as would be required of absolute formaldehyde.) The gas may be liberated from this solution by various means, but heating is not economical, as it polymerizes a large part of the formaldehyde into the insoluble and inactive *trioxymethylene* or *paraform* $(HCHO)_3$. The change also occurs somewhat on standing, but this may be prevented by chemic means (calcium salts, methyl alcohol). Trioxymethylene again yields formaldehyde by dry heat. Formaldehyde is converted into *methenamine* (hexamethylene tetramine) by ammonia.

Historical.—Formaldehyde was discovered by Hoffmann, 1867; its antiseptic action by Loew and Fischer, 1886. Aranson, 1894, showed that it also destroys toxins.

Fate.—Formaldehyde is absorbed from all parts of the alimentary tract and lungs (McGuigan, 1914). It is not excreted as such (Blum; Pohl, 1893), even with intravenous injection, unless very large doses are given (McGuigan, 1912; Impens and Rosenberg; Salkowski, 1915). It is mainly oxidized in the tissues, especially the liver (Pohl), to formic acid. The oxidation of aldehydes is not direct, but through the "Cannizzaro reaction," commonly observed *in vitro* when aldehydes are treated with alkalis, $2HCHO + H_2O = CH_3OH + HCOOH$. A part of the formic acid may appear in the urine (Pohl; Klueber and Gerlasch), but small quantities of formic acid are also completely destroyed (Sollmann, 1908). Some of the formaldehyde may be transformed into methenamine (McGuigan).

Reaction of Formaldehyde with Proteins.—Formaldehyde enters into peculiar compounds, which are precipitated under suitable conditions, from which the formaldehyde and the original proteins may be completely regenerated under other conditions. The protein is rendered more acid by binding the free amino groups. With albumoses (Sollmann, 1902) and presumably with other proteins the compound contains definite proportions of formaldehyde, albumose and alkali. It is precipitated in weakly alkaline solutions, dissolved without decomposition by stronger alkalis, and is decomposed, or its formation prevented, by weak acids and by excess of neutral salts. Even under favorable conditions the combination is completed slowly (Schryver, 1911). The precipitate contains a further quantity of formaldehyde mechanically. Formaldehyde retards or *prevents the coagulation and spontaneous laking of shed blood*, when added in the proportion of 1:200 to 400. *Uric acid and urates* are dissolved, or their precipitation is prevented, by the formation of soluble compounds. *Urea*, on the other hand, forms an insoluble compound with formaldehyde. The *digestibility* of fibrin and the coagulability of casein are diminished. Formaldehyde lessens the activity of certain *ferments*, papain, trypsin, ptyalin and amylopsin; while pepsin, rennin and malt diastase are but little altered.

Antiseptic Action.—Formaldehyde is a potent disinfectant, of relatively high penetrating power, harmless to metals, fabrics and colors and of relatively low toxicity. On account of its irritant effects, its use on the body is generally inadvisable. It is employed particularly for the disinfection of rooms and excreta.

Antiseptic Efficiency.—Formaldehyde is much more effective as a bacteriostatic agent than as a germicide. Its activity varies for different organisms. Typhoid bacilli, with exposure of twenty-four hours, are killed by 1:6000 (Hyman, 1914); all the concentrations refer to absolute HCHO. Solutions of ½ to 2½ per cent destroy all bacteria, spores and toxins, in six to twenty-four hours. The gas is similarly antiseptic, especially when it is moist. The activity is increased by acids, presumably by preventing combination with the proteins of the medium (Hinman, 1913). The germicidal efficiency against *spirochetes* is low (Akatsu, 1917).

Practical Application.—*Feces* are mixed with 10 per cent of the commercial solution. This destroys the odor almost immediately, but to insure complete disinfection, they should be left in contact for an hour. *Tuberculous sputum* should be disinfected with 5 per cent of the commercial solution for an hour. *Instruments* and other articles may be placed in 1½ to 5 per cent solutions of formalin.

Fumigation of Rooms.—No method of fumigation is absolutely reliable. Moist formaldehyde vapor is the most efficient fumigant against bacterial diseases, but has little penetrative power. It does not destroy mosquitoes or other insects, and is therefore inferior to sulfur dioxide against malaria or yellow fever (McClintock *et al.*, 1911). Formaldehyde vapor is usually generated by the heat evolved by the interaction of formaldehyde solution with permanganate or cheaper oxidizing agents.

It may also be formed by special apparatus involving the incomplete combustion of methyl alcohol or the vaporization of trioxymethylene. Simple spraying with formaldehyde solution (8 cc. per cubic meter) is also used. Evaporation of formaldehyde solution by heat is wasteful, but may be employed (150 cc. for 1000 cubic feet).

Permanganate oxidation (Evans and Russel, 1915): For a room of 2000 cubic feet, 2 pounds of potassium permanganate are placed in a 3 gallon pail which is set in a large tin can containing water. When everything is ready, 2 quarts of 40 per cent formaldehyde are poured on the permanganate, the room is vacated immediately and left closed for at least twelve hours, then thoroughly aired (Hoxie). With this and the following methods, about 40 to 80 per cent of the formaldehyde is effectively volatilized (Base, 1916; Hamilton, 1917; Storm, 1918). *Chromate method* (S. G. Dixon, 1914): A solution of 1½ fluidounces of concentrated sulfuric acid and 1 pint of U.S.P. Formaldehyde Sol. is prepared in advance. When needed, it is poured on 10 ounces of sod. dichromate crystals, which have been spread in a thin layer in a vessel ten times the capacity of the ingredients. The gas is liberated more rapidly than with permanganate; the operator must therefore withdraw promptly.

Houseflies are both attracted and killed by exposing a 1:20 dilution in saucers. They develop paralysis of the nervous system, progressing forward from the hind end of the abdomen (W. A. Hiestand, 1932).

Application to the body is not recommended because of the local irritant action. It has been employed, however, for the *disinfection of hands* (1 per cent): as a *mouth wash* and *gargle* (½ per cent); in *skin diseases* and *hyperi-*

drosis (2.5 per cent); for painting the throat in *diphtheria* or *tonsillitis* (2½ to 5 per cent). The *evaporation* of a small amount of the solution in the room has also been used in *tuberculosis*. McGuire, 1900, suggested intravenous injections of 1:20,000. They were quickly abandoned.

Formaldehyde as Food Preservative.—Concentrations of 1:33,000 to 1:20,000 have been used, especially for milk. It is both ineffective and dangerous, and is therefore properly prohibited. The ordinary concentration for milk (1:10,000) checks lactic fermentation, but does not kill the tubercle bacilli and is therefore of questionable utility. It may produce intestinal ulcers (Schaps, 1905). It probably causes cumulative effects. Even surface application is said to lead to inflammatory changes in the liver and kidneys (Fischer, 1905). Salkowski, 1915, reported that formaldehyde, 0.6 to 1 Gm. per day, added to the food of a 12 Kg. dog, was well tolerated and did not impair the utilization of protein.

Local Actions.—Formaldehyde solutions or vapor, even when very dilute, produce strong irritation of all *mucous membranes*. The susceptibility to this irritation is diminished by *habituation*. Applied to the unbroken *skin*, it hardens the epidermis, renders it rough and whitish, and produces anesthesia. Repeated application of strong solution leads to superficial *necrosis* of the skin and nails and to persistent eczema (Galewsky, 1905). Its application to broken surfaces is painful. Isolated tissues are promptly hardened. Formaldehyde is therefore used in *histologic technic* in strengths of ½ to 10 per cent. These effects are produced by the *coagulation of proteins*. They are influenced by the concentration and by the time of contact (Meneguzzi, 1913).

Urticaria.—The endermic application of formaldehyde (2 per cent) produces wheals (Sollmann, 1917). General urticaria is also sometimes seen from the systemic use of formaldehyde, in mouth-wash (Heidingsfeld, 1916) or formamint tablets (Glaser-Lipehne). Urticaria is also produced by all other nonconjugated aliphatic aldehydes, but not by conjugated or aromatic aldehydes (B. Z. Rappaport and Hoffman, 1941).

Use against Hyperidrosis.—A 20 to 30 per cent dilution of the official solution relieves excessive perspiration of the feet (Althof, 1914) or axillae. The effect is said to persist for four to six weeks after painting the area daily for three successive days; the treatment may then be repeated. If used too long, however, it tends to cause eczema. The result may also be secured by repeated anodal cataphoresis of 5 per cent formaldehyde (E. A. Pinson, 1942).

Secretin Formation.—When formaldehyde is applied directly to the mucosa of the upper intestine (not the lower), the irritation increases the flow of pancreatic juice. The most favorable concentration is 1 to 2 per cent, 8 to 10 per cent being ineffective (Delezenne and Pozerski, 1915).

Red corpuscles are fixed by dilute solutions similarly to other tissues; strong solutions of commercial (not of pure) formaldehyde may produce laking, by their formic acid (Franchi, 1913).

Spermatozoa are promptly killed by formaldehyde, 1:25,000 (J. R. Baker, 1931).

Poisoning by Swallowing Formaldehyde.—The symptoms are immediate and severe abdominal pains; often sudden and prolonged loss of consciousness and collapse. Death occurs in twenty-four to forty-eight hours. The autopsy shows severe gastritis with erosions. In nonfatal cases, the urine is suppressed for twelve to twenty-four hours, and then generally contains blood and casts. There is often diarrhea and tenesmus, sore mouth and dysphagia (MacLachlan, 1909). The recovery is curiously rapid, the patients being well within a week. The prognosis is generally favorable. Few fatilities are found in recent bibliographies (review, U. S. Public Health Reports, 1945, Suppl. 181). The fatal cases all took over 3 ounces of the commercial solution. The largest quantity from which recovery is reported is 60 cc. The *treatment* should consist in dilution and evacuation, preferably by lavage, and the administration of ammonium chloride solution, together with sodium bicarbonate or sodium phosphate as alkaline buffer. *Inhalation of formaldehyde vapor* may cause bronchitis and pneumonia, but even prolonged inhalation has little systemic action.

Intravenous injection of solutions in normal saline of a strength of 1:5000 generally produces no immediate effects, even in man, but there may be rather mild colloidoclastic reactions, which have been used against bacteremias.

Neuromuscular and autonomic reactions are modified by formaldehyde. *Striated muscle* responds to stimulation with a prolonged veratrine-like contracture, but with the action-potential persisting throughout (G. H. Bishop and Kendall, 1929). The modifications of *smo th muscle* responses were studied by Thienes. The contractibility of *heart muscle*, in frogs, is lowered by formaldehyde and acetaldehyde. The irritability is not changed (Sasaki, 1921). The antagonism to the cardiac toxicity of *nicotine* is described under methenamine.

PREPARATIONS.—***Formaldehyde Solution,** U.S.P. (Liquor Formaldehydi; Formalin); a clear, colorless, watery solution of pungent odor and caustic taste, containing not less than 37 per cent of HCOH, and some methanol to prevent polymerization. Miscible with water and alcohol. A tablespoon in a quart of water makes about 1 per cent of absolute formaldehyde. *Paraformaldehyde* (Paraform, Trioxymethylene), $(HCOH)_3$, occurs as white friable masses, or as a powder, having a slight odor of formaldehyde. Slowly sol. in cold water; insol. in alc. or ether. Dose, 0.5 Gm., 8 grains. It sublimes slowly at

100° C. and melts at 171° C. Heated under proper conditions, it is decomposed into formaldehyde and is used for the *disinfection of rooms*. Two Gm. of paraform are required per cubic meter (35 cubic feet of space). Formaldehyde is also slowly liberated at body temperature: paraform has therefore been suggested as an *intestinal antiseptic* (0.05 to 0.1 Gm. every two hours, for children), but its irritant action renders it objectionable. Larger doses (3 to 4 Gm.) are *cathartic*, small doses are rather constipating. It will not cause serious poisoning even in large doses.

FORMALDEHYDE COMPOUNDS

These are generally inactive and nonirritant in themselves, but regenerate formaldehyde under suitable conditions. It was therefore thought that they would prove valuable antiseptics. Most of them, however, liberate it either too slowly or too readily. Methenamine alone has proved really valuable.

Glutol (Schleich, 1896) is an insoluble compound of formaldehyde and gelatin, which holds the greater part of the formaldehyde so firmly that it is practically useless (Sollmann, 1908). *Other protein compounds* were also disappointing. Classen introduced compounds with *carbohydrates:* starch (amyloform), dextrin, milk-sugar, and so forth. Their fate was studied by Jacobson, 1906. There were also combinations with phenols, urea (Cohn, 1897), and others. Anhydromethylenecitrate (*citarin*) splits off CH_2O too readily (Nicolaier, 1906); methylenedisalicylic acid is not decomposed in its passage through the body (Sollmann, 1908).

METHENAMINE

Methenamine (hexamethylene-tetramine, $N_4(CH_2)_6$) is formed by the action of ammonia on formaldehyde. It is itself devoid of antiseptic, irritant or toxic actions. Its solutions, however, dissociate slowly with the evolution of formaldehyde, according to the reversible reaction $N_4(CH_2)_6 + 6H_2O \rightleftarrows 4NH_3 + 6HCHO$. This decomposition is favored by the presence of free acid; it becomes practically negligible at neutral reaction and is arrested by relatively mild alkalinity (Hanzlik and Collins, 1913; De Eds, 1924). From one-sixth to one-third of the methenamine is decomposed by the acid reactions of the digestive tract, especially of the stomach. The absorption of the remainder starts promptly, and the methenamine is distributed rapidly through the tissues and secretions, and excreted unchanged mainly in the urine. The acid reaction of the urine sets free a small quantity of formaldehyde, sufficient to be more or less antiseptic, so that methenamine is used in the prophylaxis and treatment of urinary infections (introduced by Nicolaier, 1895, 1899), especially in Escherichia coli infections that resist mandelic acid, sulfonamides and penicillin. It is useless if the urine is alkaline. Occasionally, especially in susceptible individuals, it may produce irritation of the bladder and hematuria. This is minimized by liberal dilution. Even larger doses do not cause systemic poisoning. Insignificant traces of formaldehyde are liberated in the blood and tissues; even under optimal conditions the concentration would remain far below the antiseptic level. Before this limitation was realized, methanemine was tried against infections of the bile passages, meninges, respiratory tract, accessory sinuses, and other parts. The liberated formaldehyde is oxidized to formic acid.

Time of Excretion and Distribution.—Methenamine appears in the urine within eleven minutes after oral, rectal or hypodermic administration, reaches its maximum in one to three hours, and practically ceases in four to eight hours, according to the dose. After twelve hours only small amounts are excreted, although the blood may contain faint traces after twenty-four hours (Sollmann, 1908; Crowe, 1908; Burnham, 1912; Falk and Sugiura, 1916). Approximately the same time relations obtain for its concentration and disappearance from the other secretions and tissues. Its distribution is universal, since it has been demonstrated in all parts of the body in which it was sought.

Quantitative Excretion.—With doses of 1 to 5 Gm., from 32 to 85 per cent of the methenamine is excreted by the urine. The percentage is independent of the dose (within these limits), of diuresis and of clinical conditions. It is determined mainly by the reaction that the methenamine encounters in the digestive tract, and the excretion can therefore generally be increased by the administration of alkali (De Eds, 1924). *The concentration of methenamine* depends on the dose, the time, and in urine largely on the ingestion of fluid. With continued administration three times daily, the concentration in the urine ranged from 1:1400 to 2800 for doses of 0.67 Gm.; from 1:24,00 to 14,000 for 0.33 Gm. (Falk and Sugiura, 1916). In other secretions and in the tissues the concentration is probably lower.

Excretion in Eye.—Gradle, 1911, found methenamine in the anterior chamber, its excretion being hastened by mydriatics; its concentration, however, is not sufficient to be antiseptic. In cats, Remelé, 1916, found it in the aqueous humor shortly after the intravenous injection of 2 Gm. *Excretion in milk* was announced by Bucura, 1905, and confirmed by Crowe, 1908; Woldewijn, 1910; and by J. Schmid and Schroeter, 1910. Reider, 1912, found that the highest concentration was reached after an hour. *Excretion in saliva* reaches its maximum in half an hour (Hanzlik).

Presence of Free Formaldehyde in the Urine.—The amount of formaldehyde liberated depends upon the acidity, the concentration, the time of standing and perhaps on other, unknown conditions. The liberation may occur in the kidney (Burnham) and increases in the bladder (Hinman, 1913). G. G. Smith, 1913, found that

0.5 Gm. always gave formaldehyde in acid urines, while 0.3 Gm. was inconstant. The *concentration of formaldehyde in urine* was estimated by Hinman, 1913, as below 1:40,000 in half the cases; 1:16,000 in 25 per cent; and over 1:7000 in 2 per cent of the urines. Alkaline urines do not liberate formaldehyde; but the formaldehyde liberated in the acid kidney may persist for a short time in the alkaline bladder. Kidney disease does not modify the liberation (Hinman).

Antiseptic Action.—*Methenamine itself is not antiseptic*, if the liberation of formaldehyde is prevented by alkalis (Hanzlik, 1913). A concentration of 5 per cent is required to check the growth of staphylococcus in neutral broth cultures; this may be attributed to the free formaldehyde (Jordan, 1911). The antiseptic action is always parallel to the concentration of free formaldehyde (Hanzlik and Collins). Formaldehyde in concentration of 1:50,000 to 30,000 has a distinct though limited antiseptic effect (Mossa and Paleotti).

Antiseptic effects after administration are especially marked in acid urines. Crowe, 1908, claimed that the administration of 5 Gm. per day renders the bile and other body fluids antiseptic, but exact observations have not confirmed this (Hanzlik and Collins), and the idea of producing "tissue antisepsis" by its use must be abandoned.

Therapeutic Use as Urinary Antiseptic.—Methenamine is one of the most potent urinary antiseptics, provided that the reaction of the urine is acid. It is highly effective against coli or staphylococci introduced into the bladder (E. Davis and Sharpe, 1932); although mandelic acid, sulfanilamide and acriflavine are often more successful against active bladder infections. In neutral or alkaline urine, its efficiency is practically nil (Jordan, 1911). In ammoniacal urines it would be useless. It would be especially valuable as a prophylactic, *f. i.*, in catheterization (Hinman, 1915). It was advised to prevent the spread of typhoid bacilli (Richardson, 1898), but its efficiency is doubtful. It may be used in inflammation or suppuration of the renal pelvis, bladder or urethra. The dosage should be from 0.25 to 0.5 Gm. (4 to 8 grains) in half a glass of water, four or five times a day. If the urine is alkaline, acid sodium phosphate (NaH_2PO_4) should be administered, 1 to 2 Gm. every one to four hours, as a separate prescription, midway between the methenamine administrations, until the urine is acid. This may cause moderate diarrhea.

Incompatibilities.—Methenamine is a fairly strong base, gradually displacing ammonia from its salts. It is decomposed by acids (even acetylsalicylic acid) and by acid salts with the liberation of the irritant formaldehyde. It is also incompatible with tannin, mercuric chloride and oxidizing agents (J.A.M.A., Feb. 8, 1913, p. 465).

Methenamine salts have no great advantage. Boruttau, 1914, claimed that the urinary antiseptic action is somewhat greater with salicylate or camphorate. Jacobs and Heidelberger, 1915, reported experiments with some quaternary derivatives that appear promising. The activity of these does not seem to depend on the liberation of formaldehyde, so that they are not inhibited by protein and do not require acid.

Solvent Action on Uric Acid.—Methenamine was proposed as a remedy for gout and urate calculism. It, as well as formaldehyde, dissolves uric acid, with the formation of a series of paired compounds (Nicolaier, 1906). The solvent action is really slight, however (Stevens and May, 1911), and the experimental and clinical results have been disappointing (Hanzlik, 1916).

Administration for Systemic Disinfection.—Large doses, 5 to 20 Gm. per day, were formerly administered against infections of the biliary and respiratory tracts, meninges, and so on, but critical observations do not show any antiseptic action (biliary tract, Burnham; infantile paralysis, Frazer, 1914; empyema, Shattuck, 1911). The most delicate tests have failed to detect formaldehyde in any of the tissues and secretions, other than the gastric juice and urine: negative results were reported for the milk, Schmid and Schroeter; saliva, Hanzlik; bile, cerebrospinal fluid and sputum, Burnham, 1912; various situations, McGuigan, 1912; blood and cerebrospinal fluid, Voit, 1923; blood, De Eds, 1924. Liberation under certain conditions in the aqueous humor and cerebrospinal fluid of rabbits was claimed by Sherif, 1930. The small excretion of formate is an index to the small quantity of formaldehyde liberated (De Eds, 1924).

Hematuria.—Methenamine itself is nonirritant, so that it may be given hypodermically (Gundrum, 1911) or injected into the bladder in 50 per cent solution (Burnham). After the liberation of formaldehyde, this becomes irritant, but only in specially susceptible individuals or with large doses. This results in painful micturition and eventually cystitis and hematuria. The kidneys may probably also be irritated. The cystoscope shows hemorrhagic cystitis, and postmortem examination, hyperemia of the pelvis (D. L. Simon, 1914). The hematuria has been used by malingerers (Marie and Behague, 1920). These irritant effects are exceptional if the drug is given in sufficient dilution. They disappear promptly and without any permanent damage, if it is discontinued.

I. A. Abt, 1917, believed that its use caused severe and fatal nephritis; this requires confirmation. In dogs, Wiggs, 1910, obtained marked nephritis from relatively small doses. In guinea pigs, hypodermic injections (Frothingham, 1910) produce local necrosis and gastric congestion, hemorrhage and ulceration.

Other Undesirable Actions.—Rubeolar skin rashes, catarrhs of various mucosae, and digestive disturbances have been reported (Coleman, 1903), but they are rare. Urticaria is probably fairly common. Methenamine was the most common cause of *dermatitis* in the rubber industry before 1926, so that this use has been largely discontinued (*cf.* L. Schwartz, 1934, who also discusses the other chemical dermatitis of rubber manufacture).

Intravenous injection does not seem justified in view of the rapid absorption of methenamine, but it has been used (1.5 to 2 Gm. as 25 per cent solution; Loeper and Grosdidier, 1918). Large doses may be injected without direct toxicity (Crowe, 1908; Burnham, 1913); occasional anaphylactoid reactions may be expected.

Antagonism to Nicotine.—Intravenous injection of formaldehyde (20 mg. per Kg., dogs) or methenamine, or most effectively *methenamine iodomethylate* (150 mg. per Kg.), almost immediately suppresses the auricular fibrillation and auriculoventricular dissociation of nicotine (0.1 mg. per Kg.). It also prevents the hypertension and the stimulation of isolated intestine. The action is rather special; it is much more effective than quinidine, but does not apply to other fibrillating poisons (Gautrelet, Halpern and Corteggiani, 1932). It produces some curare action (Gautrelet and Halpern, 1934).

PREPARATION.—***Methenamine,** U.S.P. (Hexamine, Hexamethylenamine, Hexamethylenetetramine), was introduced as *urotropin* and is also marketed under numerous other and confusing trade names. These commercial brands are in no way superior to the official substance (Base, 1907). It occurs as colorless, lustrous, odorless crystals, of sweet, then bitter taste. Solutions react alkaline to litmus. It is freely sol. in water (1:1.5) and alc. (1:12.5). Dose, 0.3 to 1 Gm., 5 to 15 grains. *Methenamine Tablets*, U.S.P.; usually available as 0.3 and 0.5 Gm.

Sodium formaldehyde sulfoxylate, $CH_2OHSO_2Na.2H_2O$, is a very active reducing agent, of low toxicity even with intravenous injection. S. M. Rosenthal, 1934, found it an effective antidote in *mercurial poisoning* (see Index), by reducing the mercuric to the less toxic mercurous salts.

Rosenthal, 1938, also found it effective against one strain of *pneumococci* in mice, but ineffective against other strains. This inefficiency was confirmed by H. H. Powell and Jamieson, 1935. On intravenous injection, it disappears rapidly from the blood; half to two-thirds is *excreted* unchanged by the urine, regardless of dosage, the greater part in two or three hours. *Oral administration* does not give effective blood concentrations (E. Hug, 1936). It is freely soluble in water, decomposed by dilute acids.

Nail polish dermatitis is generally caused by hypersusceptibility to *toluene sulfonamide formaldehyde* and related synthetic resins (Keil and Van Dyck, 1944).

Other Aldehydes.—All aldehydes are irritant. Acetaldehyde and paraldehyde are somewhat antiseptic, but more markedly narcotic. This narcotic action is especially prominent in trichloraldehyde (chloral).

Acroleine.—CH_2:CH.CHO, resulting from the decomposition of glycerol or fats by excessive heat, is but little antispetic. Its injection by various channels produces typical shock (G. F. Kamen, 1943). Its ordinary toxic effects consist chiefly in strong irritation of the skin and exposed mucosae. Habitual exposure seems to lead to some tolerance. No other chronic ill effects have been reported.

Heptyl aldehyde against tumors has given contradictory results. L. C. Strong and Whitney, 1938, and Strong reported softening, liquefaction and regression of spontaneous tumors, and improvement of the general condition, by the daily administration to mice in food, and to dogs hypodermically (0.1 to 1 cc.). This was confirmed by Boyland and Huntsman, 1938. C. Carruthers, 1940, reported that its application to the skin of mice on alternating days diminishes the carcinogenic frequency of methylcholanthrene, but it had no effect on established tumors. He also found (1939) that feeding of heptyl aldehyde tends to produce resorption of embryos in mice. Various other aldehydes had no effect. On the other hand, C. A. Baumann *et al.*, 1938, observed no effect on tumor growth or survival of the animals with five varieties of mouse tumors, except a nonspecific effect when enough was added to render the food so unpalatable as to restrict the caloric intake. W. G. Clark, 1939, noted no apparent effect on spindle-cell sarcoma in rats, even when the aldehyde was injected into the tumor.

OZONE

This is a polymeric form of oxygen (O_3), which decomposes readily with the liberation of active oxygen. It is strongly oxidizing, deodorant and antiseptic, but is easily destroyed in the presence of organic or other oxidizable matter. Efficient concentrations are highly irritant and produce toxic depressant systemic effects. It is used for the sterilization of water. Traces of ozone are contained in the air, especially after thunder storms, but the quantity is much too small to have any effect whatever; in fact, concentrations far beyond human tolerance are of uncertain efficiency (J.A.M.A., *57:* 1370, 1911; A. L. Kendall and Walker, 1936). At most, its persistent presence is an indicator of the absence of organic matter in the air. The odor of ozone is characteristic, disguises other odors, and tends to fatigue the olfactory endings (Wolfhugel, 1875; Erlandsen and Schwarz, 1910).

Effects of Inhalation.—The older methods of preparing ozone developed irritant nitrogen oxides. The modern machines are free from this defect. By their use, concentrations of 5 to 10 per million, inhaled for a short time, produce in man increased amplitude of the pulse, drowsiness, fatigue and persistent headache—the latter probably by irritation of the sinuses. Ten per million inhaled for fifteen minutes produces sore throat. One per million diminishes the oxygen intake and the CO_2 output. *Prolonged exposure* to concentrations below 1 per million does not produce noticeable disturbance; but with higher concentrations there is irritation of the respiratory tract and other mucous membranes, leading to fatal pulmonary edema; or in acute toxic concentrations to initial restlessness followed by depression and coma. Exposure for two hours to 10 or 15 per million is dangerous to life, but the irritant effects, cough, headache, and so forth, give ample warning to avoid the danger. For an antiseptic action, at least 13 per million would be necessary. The air contains at most 0.00015 to 0.158 per million (Jordan and Carlson, 1913).

HYDROGEN PEROXIDE

The peroxides are fairly stable in pure solutions, but on contact with catalyzers, inorganic or organic (catalase), tissues, and so on, they split off active oxygen and are therefore strongly antiseptic and deodorant. The action lasts only so long as oxygen is being evolved, and is brief and superficial. In deep and closed cavities, the rapid evolution of gas presents danger of mechanical injury and embolism. Hydrogen peroxide is employed for washing fetid wounds and ulcers; as injection for gonorrhea; as mouth wash, and for other uses. Used as the full U.S.P. strength (10 per cent of available oxygen), at least four times daily (Farrell and Nichols, 1937), it is especially effective against anaerobic organisms that grow on dead tissues, *i. e.*, fusospirochetosis, Vincent's angina, mercurial stomatitis. It is nontoxic and scarcely irritant, but for most uses it should be diluted with 2 to 10 parts of water. Its continued use as a mouth wash sometimes causes hypertrophy of the papillae of the tongue (C. S. Miller *et al.*, 1938). A stronger (30 per cent) preparation is caustic. In contact with pus it foams, and this aids mechanically in cleansing the wound. Hydrogen peroxide is a chemical *antidote* for cyanide and phosphorus poisoning. It is used for *bleaching* the hair and fabrics. The concentration of 0.35 per cent (absolute) in *milk* inhibits the development of pathogenic bacteria (Budde, 1903), but it also destroys the ferments of milk and is of questionable utility (Heinemann, 1913). Sieber, 1901, claims that it destroys toxins. The germicide action is feeble (Albert and Taylor, 1918).

Phagocytosis is stimulated *in vitro* by hydrogen peroxide, whereas free oxygen is generally depressant (H. J. Hamburger, 1915). Potassium chlorate and ferricyanide proved inactive. *Gastric acidity* is lowered by lavage with ½ to 3 per cent solutions of hydrogen peroxide, the effectiveness increasing with the concentration. The effect may persist for two weeks, but there is generally discomfort and sometimes bleeding, so that it is not a desirable clinical agent. More dilute solutions may stimulate the secretion of acid (Culmer and Atkinson, 1937). *In vitro*, hydrogen peroxide is somewhat more toxic to *ascarids* than is ascaridol (Butz and Lande, 1934).

PREPARATIONS.—***Solution of Hydrogen Peroxide,** U.S.P. (Liquor Hydrogenii Peroxidi; Solution of Hydrogen Dioxide); a slightly acid aqueous solution of H_2O_2 (approximately 3 per cent), corresponding to about 10 per cent (volumes) of available oxygen. It occurs as a colorless liquid, odorless, with slightly acid taste, producing a peculiar sensation and soapy froth in the mouth. It keeps best in bottles stoppered merely with a plug of cotton, and standing in a cool place. It is incompatible with easily oxidizable substances. It decomposes gradually. This is not due to impurities (Clover, 1913). The decomposition is retarded by small quantities of acid or acetanilid. The latter is used in most brands (Kebler, 1910), but in time these acquire a yellow tint and an odor of nitrobenzol, and should then not be used. Dose, 2 to 8 cc., ½ to 2 drachms. *Stronger Solution of Hydrogen Peroxide*, U.S.P., contains about 8 per cent of H_2O_2. It tends to deteriorate on keeping and may be stabilized by the addition of harmless substances.

"Solid Peroxide" consists of easily soluble compounds with urea, containing about 35 per cent of absolute peroxide.

Organic peroxides were introduced by Freer and Novy, 1903. Acetyl-benzoyl peroxide (Acetozone) and succinic dioxide (Alphozone) may be considered as H_2O_2 in which the H has been replaced by organic radicals. In the presence of water they are slowly hydrolyzed, forming organic peracids, with active oxidizing and germicidal properties. They were used as local and intestinal antiseptics, but are of doubtful efficiency for the latter purpose. They should not be mixed with organic liquids, or kept in a warm place, as they tend to explode.

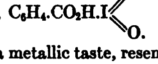
Peroxides of metals are compounds in which the H of H_2O_2 has been replaced by metals. They are readily decomposed with the formation of H_2O_2 or the active oxygen, and have been suggested as substitutes for hydrogen peroxide. The commercial products are usually mixtures containing 15 to 75 per cent of the peroxide. The compounds of the different metals vary considerably in stability and solubility, and in the ease with which their solutions are decomposed. Acids convert them rapidly into hydrogen peroxide; *f. i.*, $MgO_2 + H_2SO_4 = MgSO_4 + H_2O_2$. Water decomposes them more slowly, inversely to their solubility; *f. i.*, $ZnO_2 + 2H_2O + Zn(OH)_2 + H_2O_2$, so that their action is more prolonged. The therapeutic effect is also modified by the nature of the base. *Sodium peroxide* yields a solution sufficiently alkaline to be caustic. It is used as a paste on comedones. *Medicinal Zinc Peroxide*, U.S.P., is a fine white powder, insoluble in water, soluble in dilute acids. It is used on infected wounds, as a creamy 40 per cent suspension in water. It must come into thorough contact with the infected surface, after wide exposure and trimming (B. C. Johnson and Meleney, 1939). Zinc peroxide is also used in skin diseases; *magnesium peroxide* in dentifrices; *calcium peroxide* against gastro-intestinal fermentation.

Sodium Perborate, U.S.P., $NaBO_3.4H_2O$, yields hyrdrogen peroxide on contact with water, being transformed into metaborate which acts as a mild alkali; $NBO_3 + H_2O = H_2O_2 + NaBO_2$. It is used as a substitute for peroxide, as a dusting powder or 2 per cent solution, and especially as a dental antiseptic, and in Vincent infections, applied as a paste and rinsed off in five minutes; but its routine use is not advisable. It is strongly alkaline, producing considerable irritation and even corrosion, so that it often does more harm than good (Hirchfeld, 1937). As a mouth wash, not more than a teaspoonful should be used in a glass of water. Its continued use often produces hypertrophy of the lingual papillae and darkening of the gums (C. S. Miller *et al.*, 1938). It occurs as white crystalline granules or a white powder, soluble in water (1:40); odorless, saline taste; decomposed in moist air with the evolution of oxygen. Contains not less than 9 per cent of available oxygen. Dose, 0.06 Gm., 1 grain, U.S.P.

IODOXYBENZOIC ACID

This has a strong oxidizing action, even in the body (Heinz, 1899). Loevenhart and Grove, 1911, investigated the sodium salts of the 3 compounds: (1) Iodobenzoic acid, $C_6H_4.CO_2H.I$. (2) Iodosobenzoic acid, $C_6H_4.CO_2H.I = O$.

(3) Iodoxybenzoic acid,



$C_6H_4.CO_2H.I \begin{smallmatrix} \nearrow O. \\ \searrow O. \end{smallmatrix}$

The two latter have a metallic taste, resembling that of hydrogen peroxide, presumably due to the active oxygen. They oxidize hemoglobin to oxyhemoglobin. (2) is irritating, (1) and (3) mildly so. The systemic effects were studied by intravenous injection. (1) has little action. The oxygenated compounds (2) and (3) produce the phenomena of apnea; marked and continued fall of blood pressure by depression of the vasomotor center; brief arrest of respiration, also by depression of the medullary center. The vagus center is not affected. These actions are due to the active oxygen. This cannot replace ordinary molecular oxygen for maintaining the cardiac activity; Loevenhart and Eyster, 1913.

Antiseptic Action.—Practical results have been disappointing. (2) and (3) are much more bactericidal than (1) (Arkin, 1911). Iodoxybenzoate increased the production of antibodies in dogs (Hektoen, 1911); also the production of hemolysin and agglutinin in rabbits, when injected intravenously shortly after immunization. It stimulates phagocytosis (Arkin, 1915). Its injection lessens inflammation by mustard oil or allergy, while this is increased by cyanide, indicating that edema is lessened by oxidation and increased by asphyxia (Amberg, 1913). Iodosobenzoic acid was studied by Jahn, 1914. *In vitro* it is more effective than sulfonamides on E. coli and hemolytic streptococcus (F. P. Chinard, 1942). It reduces the toxicity of tuberculin *in vitro* (Arkin, 1916).

Iodoxybenzoic Acid against Chronic Arthritis.—Promising results were claimed, but it is now rarely used. It was reported to arrest the progress of the disease, and to remove the functional disturbances, to relieve the pain, diminish the swelling and tenderness of the joints, to increase their mobility and functional use, and to improve the general health (A. G. Young and Youmans, 1926). The ammonium salt is administered intravenously, 1 Gm. in 100 cc., injected slowly (ten minutes) once or twice a week, for 6 to 8 doses. The toxicity is low, and is determined mainly by the rate of injection. At most, there may be temporary apnea. The solution is irritant, and may produce fibrosis of the vein; if it escapes into the subcutaneous tissue, it is painful, but not escharotic. The mechanism of action is not understood. The injections are often followed by irritation of the mucous membranes and presumably of other tissues; it is possible that it sets up acute inflammatory reaction in the joints, which may sometimes lead to improvement of the chronic process.

BORIC ACID AND SODIUM BORATE (BORAX)

These are fairly antiseptic, but not potently germicidal, and it is questionable whether they check bacteria under clinical conditions. They are not deleterious locally or systemically in the amounts ordinarily used on small areas, but larger doses are fatal. Boric acid is a mild astringent, through its acidity. Sodium borate is a mild alkali and dissolves mucus. Its alkalinity makes it incompatible with alkaloids, local anesthetics, salts of metals and with acacia. Boric acid is employed in surgery as dusting powder, as saturated (4 per cent) aqueous solution, as boroglycerite and in collyria (2 per cent of boric acid, which may be buffered with 0.5 per cent of sodium borate). A 25 per cent paste of borax in glycerol or honey is painted on ulcers of the mouth or gum, as in thrush, four times daily. Dusting with boric acid powder, 10 per cent in talcum, is among the most effective measures for the prevention and treatment of ringworm of the foot (Weidman *et al.*, 1945). The borate ion has no other therapeutic uses. Boric acid and borax have been employed as food preservatives. Small single doses are generally innocuous; their continued use produces slight but cumulative effects, so that their employment is not advisable. Directly harmful effects follow doses of 2 to 5 Gm. of boric acid or borax, and 15 to 30 Gm. may be fatal (Schwyzer; C. Potter, 1921).

Occurrence.—Minute traces of boron occur in all animals, most abundantly in the oceanic (Bertrand and Agulhon, 1912). *Plants* also take it up readily from the soil (Cook, 1916), and it appears to be necessary for several growth functions, especially cell division, in addition to making iron more available (W. L. Powers, 1939). Small quantities produce marked increase of growth (of beans, Fagundes, 1934; flax in nutritive media, optional concentration = 0.5 mg. per liter, Skolnick, 1933). Somewhat higher concentrations (but still dilute) cause spotting of the leaves (Haselhoff, 1913).

Seedlings of a variety of plants, when grown in nutrient solutions, soon die unless the solution contains 0.3 to 3 mg. of boron per liter, varying with the species (Skolnik, 1935). *Animals* do not appear to require it; at least, addition of boron to a boron-poor diet does not improve the growth of rats (Hove *et al.*, 1939). However, boron lengthens the survival time of rats on potassium-deficient diet (J. T. Skinner and McHargue, 1945).

Antiseptic Efficiency.—Boric acid is not a disinfectant. Even saturated solutions do not kill bacteria. Solutions of 0.3 per cent check putrefaction and decomposition, but not the growth of pathogenic organisms (Bernstein, 1910). The antiseptic efficiency varies for different bacterial cultures. It begins with about $\frac{1}{10}$ saturated; and for most is complete with about $\frac{1}{4}$ saturated (Tanner and Funk, 1919). Borax is somewhat less efficient. Their popularity as food preservatives is attributable to the absence of distinctive odor and taste. The acid is used in meats in the concentration of 0.5 per cent; in milk, of 0.2 per cent. Borax and the insoluble calcium borate kill *house fly larvae* in manure (Cook and Wilson, 1917), but it may render this toxic to plants. As a general *insecticide*, sodium borate is considerably less effective than fluoride (G. D. Shafer, 1915).

Borate Buffered Eyewaters.—The *p*H of eyewaters should be adjusted to their constituents. Zinc sulfate and epinephrine may be dispensed in boric acid, 1.24 per cent, NaCl 0.29 per cent, approximately *p*H 5.3. Neutrality (*p*H 7.1) is obtained with boric acid, 1.24, sodium borate, 0.13 per cent; alkalinity (*p*H 8.3) with boric acid, 0.8, sodium borate, 0.6 per cent.

Acute boric poisoning has occured rather frequently by intravenous injection of boric acid solution in mistake for saline; by similar mistakes in infant feeding (C. G. Barnum, 1945); by flushing serous cavities; by enemas, and by the application of powdered boric acid or boric ointment to extensive burns and eczemas (E. H. Watson, 1945; review, C. C. Pfeiffer *et al.*, 1945).

The symptoms develop rather slowly, beginning about eight hours after ingestion, with vomiting, diarrhea, rapidly progressing prostration; then convulsive tremors, meningismus, convulsions, exfoliative dermatitis ("boiled lobster" erythema), ending in a progressive shock syndrome. Death may occur in about thirty-six hours, from 2 to 5 Gm. of boric acid or 15 to 30 Gm. of borax. *Pathologic changes* consist in focal hemorrhages, vascular engorgement and leukocytic infiltration of the skin; degeneration of the renal tubules; rather insignificant fatty parenchymatous degeneration of the liver. The most characteristic changes are neurophagia and hypochromatosis in the brain and spinal cord, produced by a third of the MFD, and by the application of the 10 per cent boric acid ointment to burns of 4 per cent of the body surface. Boron can be demonstrated in both white and gray matter of all parts of the central nervous system and in the peripheral nerves. It is not combined with phospholipids or cholesterol. It accumulates also in the liver and body fat. *Treatment* of boric poisoning is by evacuation, and large intravenous injection of Ringer's solution or plasma (Pfeiffer *et al.*, 1945).

Boric Acid Hemolysis.—Blood corpuscles suspended in 1 per cent boric acid do not undergo any visible change; but their osmotic properties are altered, so that they become laked if transferred to isotonic salt solutions. This alteration is due to the presence of boric acid within the cells, for laking does not occur if the corpuscles are washed in hypertonic salt solutions (Kosakai, 1919).

The **effects of small doses** of boric acid and borax, such as are used in preserving foods, would not be serious, even if the consumption were continued for a long time. However, the results are somewhat deleterious in normal individuals, and they would probably be more so in patients with digestive or renal disturbance. A man living largely on preserved food may ingest as much as 0.5 Gm. of boric acid (or its equivalent in borax) per day; the consumption would generally fall below this figure, but could rise to several grams. All investigators agree that quantities to 0.5 Gm. have no immediate action of any kind in healthy individuals. When the consumption is continued for a long time, boric acid seems to have a *cumulative action* on digestion and absorption, metabolism and the kidneys (Forster, 1883; Rost, 1905; Wiley, 1904). The digestion becomes somewhat deranged; the body weight decreases; the feces become more watery. If a slight albuminuria was present, this is increased (Wiley). The cumulative effect may be explained by the observation that the *excretion* of boric acid is slow, requiring several days, although it begins within ten minutes, and reaches its maximum in the second hour. With continued daily hypodermic injections of 200 mg. per Kg., fourteen to eighteen days are required to reach a urinary plateau (Pfeiffer *et al.*). On the average, 15 per cent is retained, the other 85 per cent being excreted mainly by the urine, to a slight extent by sweat and milk, and practically none by the feces (Wiley). The excretion is not hastened by diuresis (Rost, 1905). A trace occurs normally in milk and eggs (Bertrand and Agulhon, 1913); it is increased materially by the addition of boron to the food. It also passes through the placenta to the fetus (Hove, Elvehjem and Hart, 1939).

Somewhat larger doses, 1 to 3 Gm. per day, produce the described effects more rapidly and more severely Headaches appear. With 5 Gm., the subject soon becomes unable to do any work. Quantities above 2 Gm. per day should be condemned as distinctly harmful. The growth of immature rats is retarded by 0.25 per cent of boric acid in their drinking water, but not by 0.1 per cent (Pfeiffer *et al.*). Harrington, 1904, observed that the continued administration of borax to cats leads to severe kidney lesions. The internal use of boric acid (against *obesity*) sometimes produces *skin disorders* resembling pityriasis (Memmesheimer, 1935). Kahlenberg and Barwaser, 1928, reported that boric acid is promptly *absorbed from the skin*, but others have been unable to confirm this (Pfeiffer *et al.*, 1945). The actions on the *uterus*, which are not very marked, were investigated by J. W. C. Gunn, 1920.

PREPARATIONS.—***Boric Acid**, U.S.P. (Boracic Acid), H_3BO_3; translucent colorless scales, or light, fine, bulky powder, unctuous to the touch; odorless; of slightly saline taste. Slowly sol. in water (1:18); sol. in alc. (1:18); freely sol. in glyc. (1:4). Dose, 0.3 to 1 Gm., 5 to 15 grains, as urinary antiseptic. Locally, in lotions, injections, gargles, and the like, 2 to 4 per cent (1½ to 3 teaspoons per pint). A saturated watery solution contains about 5 per cent, or 25 grains per ounce. *Glycerite of Boroglycerin*, U.S.P., contains about 50 per cent of boroglycerin, $C_3H_5BO_3$, prepared by heating boric acid and glycerin. It is used externally, diluted with ten parts of water. *Boric Acid Ointment* contains 10 per cent. *Liquor Antisepticus*, N.F., contains 2.5 per cent of boric acid, and aromatic oils. A number of proprietary mixtures, *e. g.*, "listerine," have a similar composition. Their antiseptic efficiency is slight (Verhoeff and Ellis, 1907).

* **Sodium Borate,** U.S.P. (Borax), $Na_2B_4C_7.10H_2O$. Colorless, transparent crystals, or white powder, odorless, of sweetish, alkaline taste. Sol. in water (1:16), with alkaline reaction; very sol. in glyc. (1:1); practically insol. in alc. *Incompatible* with alkaloids, acids, mucilage of acacia. (Free boric acid is not incompatible with most alkaloids.) Dose, 0.3 to 1 Gm., 5 to 15 grains.

◆

THEORIES OF NARCOSIS

The neutral aliphatic hydrocarbons resemble each other in their main actions. Their most conspicuous effect on the higher animals consists in stupefaction, passing with larger doses into insensibility and motor paralysis; *i. e.*, into profound narcosis or anesthesia of central origin. Analogous narcotic or depressant effects are produced on all forms of protoplasm and on unorganized ferments. Hemolysis is also a marked effect.

The term "narcosis" is applied in biology to reversible decrease or abolition of the normal cell activities by agencies that are not highly selective. It may be produced by a variety of physical and chemical conditions: by cold, fatigue, electric inhibition (anelectrotonus), oxygen deficiency, certain ions and strikingly by the neutral aliphatic derivatives used clinically as general anesthetics, hypnotics and sedatives. Various attempts have been made to explain the fundamental nature of narcosis, and particularly to correlate it with the composition and with the other chemical and physical properties of the narcotics. The results indicate that there are striking quantitative relations between the narcotic strength of the hydrocarbon series and their lipoid and surface affinity. The efficiency increases with their solubility-partition coefficient (Meyer-Overton Law), which is an index of the lipoid affinity; and with their depressive effect on the surface tension of water, which is an inverse index of surface affinity (I. Traube). The lipoid and surface affinity are generally parallel; when they conflict, the narcotic efficiency appears sometimes to follow the one, sometimes the other. Both properties tend to condense the narcotic agent on the surface of the cell; their relative share in this is determined largely by the amount of lipoid in the cell membrane. The condensation of the agent on the cell surface has at least three effects: (1) it increases its potency by increasing its concentration; (2) the reduction of surface tension alters the distribution of solutes and the electric potential in the cell; and (3) this, together with the adsorption of the lipolytic substance into the lipoids of the cell membrane, alters its *permeability*. This is decreased at first, interfering with the increase of permeability involved in stimulation. This appears to be the essential cause of the narcotic action. If the action progresses too far, the cell may be disorganized, injured or killed, in which case the permeability increases. Other narcotic agents produce analogous changes in permeability, possibly through different mechanisms. At all events, the action of the aliphatic narcotics is on the cell surface and not on the cytoplasm; for they do not produce narcosis if they are injected into the interior of amebae (Marsland, 1934). Quantitatively similar actions are produced on enzymes, suggesting that the chief factor of aliphatic narcosis is the "blanketing" of the reacting surface (Warburg). Other theories of narcosis will be discussed in the small type.

Influence of Chemical Structure.—The earlier studies indicated that the actions of this series appear to be influenced by the chemical structure, and much labor was expended on determining the share of various side chains (Binz, 1881; Baumann and Kast, 1890). The results seemed to show certain relations, but the generalizations did not stand the test of wider experience (Meyer, 1899; Kionka, 1900). The chemical structure affects the narcotic action only indirectly, by modifying the partition coefficient and the surface affinity, which vary in a definite manner with changes in composition. Special side chains may be responsible for side actions; chlorine compounds are peculiarly toxic to the heart.

The *empiric relations* are practically interesting and important, although they have lost theoretical significance. The following conclusions appear justified: other things being equal, the strength of action increases with the length of the chain. A limit is soon reached, however, for the drugs become less volatile, less soluble and less absorbable the higher they stand in the series; so that the higher paraffins are entirely insoluble and inactive. With normal alcohols the narcotic potency for *tadpoles* increases to C_{12} and decreases beyond C_{14} (K. Meyer and Hemmi, 1935). *Hemolysis* by straight-chain alcohols increases linearly with the log of the number of carbon atoms (Ponder and Hyman, 1939). *Inhibition of phagocytosis* increases with the molecular weight of primary alcohols, but decreases with amyl, hexyl and heptyl alcohols (H. Welch and Slocum, 1943).

The ethyl radical, C_2H_5, seems best adapted to therapeutic purposes. The action may be modified by replacing the H of the group by other elements or groups. The compounds so formed all possess the typical action of the hydrocarbon group; but this may be so overshadowed by other actions as to be scarcely appreciable. A good example of this is the introduction of the group NO_2. This acts much more strongly than the hydrocarbon part of the molecule, and consequently the nitrite action is obtained before there can be any hydrocarbon action. The same is true if we substitute an aromatic radical. The introduction of certain other radicals weakens the hydrocarbon action to a great extent, especially the acid-forming radical CO_2H. The introduction of hydrocarbon radicals into an amine molecule destroys their action entirely. The introduction of more than one OH group also weakens or destroys the action. Aldehydes and ketones are more active than the corresponding alcohols. The introduction of the halogens, and especially of Cl, often enhances the action, but this is not proportional to the number of Cl molecules introduced. The introduction of O (ethers) also increases the action. The introduction of acids (esters) weakens it.

Lipoid Affinity of Narcotics.—Bibra and Harless, 1847, shortly after the discovery of anesthesia, drew attention to the fact that practically all fat solvents are narcotics, and suggested that they dissolve the fats out of the nerve cells. The difficulty of explaining the rapid recovery proves that this theory cannot be correct, and it was accordingly abandoned; but later workers continued to point out more or less quantitative relations. Hermann, 1866, *f. i.*, showed that all the aliphatic narcotics dissolve red blood corpuscles, connected this with their lipoid solubility, and first suggested the modern lipoid theory. Conversely, Richet, 1895, argued that the narcotic efficiency is inversely proportional to the solubility in water. The relations observed by Hermann and by Richet were striking but not conclusive. It was only by their combination that an exact quantitative relation could be demonstrated. This was done, independently and practically simultaneously, by H. Meyer and by Overton, 1899 and 1901. They showed a close parallelism between narcotic efficiency and the "partition coefficient": $\frac{\text{Solubility in fat } (S_F)}{\text{Solubility in water } (S_W)}$ usually determined on olive oil. The higher this coefficient, the more powerful the narcotic action ("*Meyer-Overton Law*"). The parallelism occurs so frequently that it must be assumed that the lipoid affinity as expressed by this coefficient is concerned in some way in the narcosis. There are, however, exceptions which indicate that it is not the only factor.

Objection has been made to the olive oil coefficient (Moore and Roaf, 1906), since the cell lipoids, especially in the nerve tissues, include lipoids of quite different solubility characters, such as cholesterol and the phosphatides, lecithin, cephalin, cerebrin, cerebrosides, and the like (W. Koch, 1911). This would affect the degree rather than the direction of the relation. Closer approximations are obtained with olein-alcohol, $C_{18}H_{35}OH$, whose solvent properties closely resemble those of the spinal cord lipoids (K. H. Meyer, 1935).

Evidence for the Meyer-Overton Law.—The narcotic concentrations have been determined mainly on tadpoles; but the law has also been tested on other animals, plants and tissues, with general agreement, but with some differences (review, M. Kochmann, 1936). Fuehner, 1909, investigated the influence of *mixed narcotics*, and found that the coefficient and narcosis were always modified in the same direction. The serial relation of aliphatic alcohols and other aliphatic derivatives was studied on the *frog heart* by A. J. Clark, 1930; on the *ciliary movements* of the gills of oysters, by S. Nomura, 1928. The relation applies also to other properties than narcotic action; for instance, to *local irritation* (A. Rikl, 1928). *Exceptions to the Meyer-Overton law* may occur from complicating factors. The influence of *temperature* on narcotic efficiency is not always parallel to the partition coefficient or to the surface tension. Hoeber, 1919, found that the relation between temperature on narcosis and partition coefficient does not hold for muscle and nerve. In tadpoles, the susceptibility to the narcotics undergoes interesting changes with the *development of the animals* (Vernon, 1913). The critical concentrations also vary for different tissues; indeed, for different functions of the same tissue, so that it is unsafe to generalize widely. It is also sometimes difficult to differentiate between narcosis and other forms of injury. *The Meyer-Overton law applies only to the aliphatic narcotics.* Morphine and other basic and saline narcotics do not obey the law, and must act by entirely different mechanisms.

Influence of Extraneous Fats on Narcosis.—It might be expected that narcosis would be affected by fatty tissues, deflecting a certain amount of the anesthetic; but this does not seem to be the case to a notable degree; presumably the cell walls of adipose tissue are not easily permeable to lipoids.

Mansfeld, 1905, suggested that the low resistance of starved animals is due to this. The theory is not convincing, for in starvation the resistance is lowered in many other directions. Cloetta, 1907, tried the converse experiment, the influence of increasing the fatty tissue. His results do not justify general conclusions, but previous injection of *cholesterol* materially increases the depth of anesthesia by ether or barbiturates (Starkenstein and Walden). *Lecithin* does not have this effect, although it has about the same solvent-affinity for ether (Foldes and Beecher, 1943).

Quantitative Distribution of Narcotics in Brain.—The total amount absorbed into the brain substance depends largely on the mass of myeline sheath, neuroglia, and so forth, which are not involved in narcosis. For this reason, the relative amount of narcotic found in different parts of the brain does not furnish a clew to the site of action (Meyer and Gottlieb, 1936).

Surface Affinity.—The close parallelism of narcotic concentration and the depressive action on the surface tension to water was pointed out especially by J. Traube, 1904–1928, and Czapek, 1911, There is a similar parallelism between the surface tension effect and the partition coefficient, so that it is difficult to generalize as to which property is the determining factor in the narcosis. There appear to be more exceptions to Traube's rule than to Overton's (Lillie, 1916), but attempts to distinguish between them are not conclusive (review, M. Kochmann, 1936). Presumably both properties participate, to a varying extent in different tissues. Diminution of the surface tension of the plasma during ether anesthesia can be demonstrated on intact mammals (Trabucchi, 1928)

Fuehner, 1912, found that for *hemolysis*, and for animals devoid of a nervous system, the efficiency of homologous alcohols is parallel to the surface tension; but in proportion as the nervous system develops, the activity of the higher alcohols becomes relatively greater, and agrees better with the partition coefficient. With chlorine derivatives, the hemolytic action increases with the chlorine content and with the molecular weight, without relation to the surface tension (Plotz, 1920). The depression of *frog heart* by serial homologous alcohols follows a biphasic curve which parallels closely their effect on surface tension (A. J. Clark, 1930).

The **permeability of cell membranes** is diminished by narcotic concentrations, and increased by toxic concentrations.

In nerve fibers and in muscle, Hoeber, 1915, found that low concentrations of anesthetics decrease permeability, preventing the swelling which normally occurs in solutions of potassium salts. High concentrations increase the permeability; this would correspond to a toxic effect. Both phenomena have been confirmed on fish eggs by McClendon, 1915. Osterhout, 1912, 1918, showed that anesthetics decrease the electric conductivity, and therefore the permeability, of plants. Fatal concentrations again increase the permeability. Hemolysis also is an instance of increased permeability by toxic concentrations (Hoeber, 1915; Joel, 1915) The *relation of depression and stimulation to permeability* was illustrated by R. S. Lillie, 1912, on Arenicola larvae. Similar phenomena are observed in the effects of anesthetics on the sensitive plant.

Relation of Cell Permeability to Stimulation.—The decrease of permeability by narcotic concentrations interferes with the changes of permeability which are necessary for stimulation; according to the views of Nernst (1899), stimulation depends on a change in the electric polarization of the cell, due to a change in the concentration of the ions at the surface, brought about by a sudden increase of the permeability of this membrane at the moment of stimulation. This change is hindered when the permeability is decreased by the narcotics (review, R. S. Lillie, 1915). Changes in the plasma membrane could also be effected by other means, and the narcotic effects of salts can be explained in this manner. A plausible explanation of the actions of morphine and most of the local anesthetics is still lacking.

Anesthetics on Artificial Osmotic Membranes.—Lipolytic agents increase the electrical resistance of artificial membranes impregnated with lecithin; *i. e.*, they diminish the permeability to ions (S. Loewe, 1913). They also decrease, reversibly, the permeability of copper ferrocyanide and of collodion membranes, the lower homologues being more effective for ferrocyanide, the higher for collodion (Anselmino, 1928). Analogous phenomena are observable in artificial systems of phosphatide and salt solutions (J. Loeb and Beutner, 1913).

Pilocarpine Adsorption by Serum.—Serum adsorbs pilocarpine hydrochloride so that it does not diffuse through parchment. Addition of alcohol and other lipolytic agents displaces it so that diffusion occurs. However, the maximal efficiency in homologous series does not coincide with the maximal narcotic potency, indicating that such adsorption is not the fundamental cause of narcosis (Beutner and Hyden, 1929).

Excitability and Conductivity of Nerve.—Narcosis of a nerve, however produced, always lowers both these functions in strict parallel (Verworn, Erregung and Laehmung, p. 121). While a normal nerve conducts without loss of stimulus, a narcotized nerve shows a decrement during conduction (*ibid.*, p. 127). The narcosis of nerve structures, unlike that of skeletal muscle, follows an "*all or none*" *law*, so that any concentration that is effective at all produces complete inexcitability, if it is sufficiently continued. This holds not only for lipolytic agents, but also for heat and for curare (Mansfeld; Somlo; v. Szirmay; 1923). *Narcotized skeletal muscle* fails to respond first to electrical, then to thermal, and finally to chemical stimulation (Tissot, 1894); but this is conditioned on the strength of the stimulus (H. T. Graham, 1929).

Phagocytosis is stimulated by minute doses of lipolytic agents, parallel to their partition coefficient, probably explained by lowering of surface tension. Narcotic concentrations paralyze the movements of leukocytes (Hamburger and de Haan; Bubanovic, 1911).

Coagulation, Precipitation and Flocculation Theories.—Aliphatic narcotics generally tend to coagulate and precipitate proteins and other hydrophilic colloids, but this requires considerably higher concentrations than are attained in ordinary anesthesia. Claude Bernard in 1853 and 1875 suggested that narcosis might be due to some kind of reversible semicoagulation, perhaps analogous to the muscle rigor produced by chloroform. He did not furnish experimental evidence for the suggestion. Others have recurred to it time and again (Binz, 1891), and W. D. Bancroft and associates, 1931, shifted the ground to flocculation, but their evidence is also unconvincing (V. E. Henderson and Lucas, 1932). Indeed, the known effects of flocculation, as witnessed, for instance, in anaphylaxis, are quite the opposite of narcosis.

Bernard, 1875, based his suggestion on the observation that muscle exposed to chloroform or ether until it is paralyzed, but not in rigor, loses its transparency under the microscope. Binz (Lectures, 1891) reported that the cells of fresh brain sections are "coagulated" by solutions of chloroform or morphine, but this required concentrations never present in the living brain (for instance, 1 per cent of morphine); and even with these, his results have not been reproduced by others. Marinesco claimed that chloroform causes flocculation in cells, confined to the nucleus; but he also used fatal concentrations. Meantime data accumulated on the *effects of lipolytic narcotics in vitro*. Handovsky and Wagner, 1911, and A. Thomas, 1915, observed that they increase the *viscosity of lecithin suspensions, and the precipitability* of these by electrolytes. It is not safe, however, to generalize from this, for Hoeber and Gordon, 1914, reported that the anesthetics hinder the precipitation of lipoid suspensions by calcium; and W. Koch, 1910, showed that the various lipolytic anesthetics differ in their effects on the aggregation of the phosphatides. The anesthetics affect *lipoid emulsions* so as to promote the continuity of the fatty phase, and this shows a general parallelism with the narcotic phenomena (Clowes; M. Fischer and Hoskin, 1916). I. Traube and Klein, 1921, showed that the lipolytic anesthetics exist in watery solutions largely as colloids (as do also other difficultly soluble substances), and as such they tend to accumulate at the interface, and to produce *flocculation and precipitation of other colloids*. The adsorption of the anesthetics on colloids also explains the observation of Moore and Roaf, 1905, that the *solubility of chloroform in serum and tissue extracts* does not obey the ordinary laws of solution. The adsorption is not very firm, however, for Cushny, 1910, found that the *exhalation* of the volatile members of the alkyl series is exactly analogous to their evaporation from watery solutions.

Bancroft and Richter, 1931, reopened the subject with more delicate physical methods and reported *ultramicroscopic flocculation in vitro* with dilutions more nearly comparable to those occurring in life, and claimed to have observed changes of viscosity in the living. Changes of viscosity and even opacity in *living cells* as the result of chloroform, ether, and the like, have also been described by Frederikse, 1933, and Koehring, 1933, but they generally involved fatal concentrations; nor are changes in the viscosity or transparency characteristic of narcosis, for they occur with changes of *p*H (Rosenfeld and Weinberg, 1932, tissue cultures), in muscular contraction, and in the process of dying. Bancroft and his associates, however, asserted dogmatically that irritability is increased by imperfect and depressed by further flocculation; that decreased viscosity causes reversible, and increased viscosity irreversible, narcosis; that all narcotic effects are due to flocculation while solvent ions act as stimulants; and that mental disease, drug addiction, sciatica, old age and chicken cholera are also due to this flocculation, which they claimed to resolve with thiocyanate (Bancroft and Russler, 1932). V. E. Henderson and Lucas, 1932, pointed out the weakness of the deductions, and Birkholder, 1932, the errors in the experimental evidence.

Dubois, 1894, observed exudation of water in narcotized plant cells, and suggested that narcosis consists in *dehydration*. Overton, however, showed that the phenomenon is a manifestation of irreparable injury, and not of narcosis.

Verworn's Theory of Oxygen Deprivation.—Verworn, 1909 (Harvey Lectures, 1911), pointed out that narcosis is generally accompanied by diminished oxidation, and that deficiency of oxygen produces anesthetic phenomena. He therefore suggested that narcosis is due to interference with oxygenation, to incapacity of the cell substance to undergo oxidation, even in the presence of oxygen, while nonoxidative destruction proceeds unchecked. Verworn's facts do not prove the theory, for since narcosis suppresses irritability, it would naturally depress oxidation; this would be the effect instead of the cause of the narcosis. Conversely, the suppression of irritability by oxygen deprivation does not prove that every narcosis must be due to oxygen deprivation. This could be accepted only if interference with oxidation and narcosis were always strictly parallel. This is not the case.

Anesthetic Effects of Oxygen Deprivation.—The anesthetic effects of asphyxia have long been familiar. Frogs perfused with saline solution become inexcitable, but the excitability is preserved or reappears if the solution is oxygenated (Verworn, 1900). Similarly, excised nerve loses its excitability in an atmosphere free from oxygen (Froelich, 1904). Mansfeld, 1909, showed that the results are additive; the paraldehyde narcosis in tadpoles is increased by degrees of oxygen deficiency which are in themselves harmless. On the other hand, there are instances (nerve trunks, vorticella, cilia) in which oxygen deprivation acts slowly, while anesthetics act promptly. HCN, which is a strong asphyxiant, is a weak anesthetic. Anaerobic organisms are also subject to narcosis, showing that this has nothing to do with free oxygen or its penetration into the cells.

Respiration of Excised Nervous Tissue.—Anesthetic concentrations of ether and other anesthetics have no effect on the oxidation of dextrose by slices of cerebral cortex (Jowett, 1938; F. N. Craig, 1943); but higher concentrations inhibit the oxidation of glucose, lactate, pyruvate, and somewhat of glutamic acid; not of succinate or p-phenylene diamine. Oxidation by yeast is not inhibited by these concentrations (Quastel and Wheatley, 1934). Herter found that the oxidizing capacity of tissues for methylene blue is greatly diminished in anesthesia. Vernon, 1909, claimed a quantitative relation between the hemolytic effect of alcohols and their influence on the respiration of excised kidneys. Tashiro, 1913, found that anesthetics greatly diminish the CO_2 output of nerves. Warburg, 1910, and Loeb and Wasteneys, 1913, found the oxygen consumption normal in narcotized sea urchin eggs.

Indole furnishes a strong argument against the explanation of narcosis by oxygen deprivation. It is a potent inhibitor of brain respiration in rats, but its administration leads to convulsions, not to narcosis, although the blood contains enough of the poison to lower brain respiration *in vitro* by a third to a half. Narcotic concentration of barbiturates does not decrease brain respiration significantly, *in vivo* or *in vitro* (M. C. Hutchinson and Stotz, 1941).

Reduction of flavoprotein and cytochrome into inactive complexes has been suggested as a possible basis of the cerebral narcotic action (M. E. Greig, 1946).

Blood Catalase.—Burge, Weill and Ashman, 1918, claimed that narcosis is accompanied by a decrease of the catalase content of the blood, roughly parallel to the depth and rapidity of the anesthesia; but with a more reliable method, Becht, 1919, found practically no change of catalase during anesthesia; if anything, there was a slight increase. There is no evidence that the catalases have anything to do with the ordinary processes of the body. More probably, they serve to destroy peroxides that might become harmful (Loew).

Unorganized Ferments.—The lipolytic narcotics retard the action of ferments in general, by being adsorbed on the active surface of the enzymes (Warburg, 1927); for instance, zymase (Warburg and Wiesel, 1912); yeast invertase (Meyerhof, 1914); oxidase (Vernon, 1912); of pepsin, rennin, trypsin, and so on; of colloidal platinum (Meyerhof); activated blood charcoal and other inorganic catalysts. The relative activity is similar to that for protoplasm; but the concentrations required for the unorganized ferments are considerably greater than the concentrations that suffice for the narcosis of living protoplasm, so that they cannot be transferred directly. The *luminescent* reaction of purified luciferin and luciferase is retarded *in vitro* by urethane, sulfonamides and p-aminobenzoic acid, without affecting the total luminescence produced (F. H. Johnson and Chase, 1942).

Cerebral Anemia.—The analogies of narcosis in the higher animals with the phenomena of natural sleep suggested a common origin to the earlier investigators. Since sleep was then explained by cerebral anemia (Durham, 1860), the same explanation was adopted for narcosis (Bedford-Brown, 1860). It was subsequently found, however, that changes in the cerebral circulation are small and variable (Cl. Bernard, 1875).

All the theories of *deficient nutrition of the brain*—whether through anemia or otherwise—are disproved by the fact that narcosis can be induced in frogs in which all the blood has been displaced by saline solution, or in which the cerebral circulation has been arrested; in excised nerve-muscle preparations; in animals which do not possess blood; in plants; and even in unicellular organisms.

Morphologic Changes.—Diminution and fusion of the *Nissl granules* have been described by good observers after deep anesthesia; other observations have not been able to confirm this, and the changes may be only artifacts. Kocher, 1916, emphasized the numerous sources of error and the inconstant results of such observations. It is also stated that the dendrites of many pyramidal cells show moniliform enlargements; the alterations disappear completely within forty-eight hours, even when caused by chloroform anesthesia of nine hours' duration. Lépine and Duval attributed anesthesia to retraction of the dendritic processes.

Temperature Narcosis.—Claude Bernard pointed out that reversible narcosis can be produced in frogs by careful warming; and G. H. Parker, 1939, found that surgical anesthesia of cold-blooded animals can be secured by packing them in cracked ice for ten to fifteen minutes, with quick recovery on warming.

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ALCOHOL

Ethyl alcohol is a local irritant. After absorption, it depresses the central nervous system, especially the "higher functions." It simulates stimulation, chiefly by lowering the normal restraining functions; but there may be some direct facilitation of motor processes and respiration. The psychical symptoms show individual differences according to temperaments and circumstances, but they tend to run an ascending course with increasing doses, through euphoria, comfort and enjoyment, to elation and vivacity; then downward through loquacity, garrulity, emotionalism either affectionate or quarrelsome or both, to violence, then hebetude, stupor and finally coma. Motor symptoms run through a similar but not necessarily parallel course.

"Stimulant" Effects of Alcohol.—These, as observed in most individuals after taking "moderate" doses of alcohol, appear at first view typical of stimulation. There is an increase in the rate of the *respiration* and of the *heart;* the *blood pressure* rises. The *skin* is reddened, with a grateful sensation of warmth and comfort. There is an increased *vivacity* of motion, action and speech, which later may acquire a stamp of brilliancy, perhaps of inspiration. The *subjective condition* generally veers toward self-appreciation. Shyness, if it ordinarily exists, is replaced by self-confidence. The person under the influence of alcohol feels an unlimited confidence in his own powers and accomplishments, both intellectual and physical. He attempts difficult and impossible tasks, and feels that he accomplishes them. He may similarly overestimate the performance of others.

No better description of these effects has been given than that of Horace: "What wonders does not wine! It discloses secrets; ratifies and confirms our hopes;

thrusts the coward forth to battle; eases the anxious mind of its burthen; instructs in arts. Whom has not a cheerful glass made eloquent! Whom not quite free and easy from pinching poverty!"

These manifestations are so conspicuous and apparent that alcohol in proper doses has been considered a typical stimulant. However, the critical study of its actions tends to the conclusion that *most of these actions do not depend upon true direct stimulation* of the nerve centers, but that they are the indirect result of incoordination, of accessory factors of environment, and of reflex stimulations.

Of the physical phenomena, the *flushing of the cutaneous vessels*, and its attendant sensation of warmth, are due to central vasomotor depression. The *quickened pulse* results partly from reflexes caused by swallowing and by irritation of the mucous membranes, partly from the emotional excitement and increased movements; not at all from a direct action on the cardiac nervous or muscular mechanism—for it is absent in animals, and very brief in man if the factor of excitement be eliminated. The *quickening of the respiration* is largely due to similar causes.

The *psychic phenomena* are explained chiefly by dulling of certain mental faculties while others are still practically unaffected, resulting in disturbance of the "normal balance of the brain." The first functions to be lost are the finer grades of judgment, reflection, observation and attention—the faculties largely acquired through education, which constitute the elements of the restraint and prudence that man usually imposes on his actions. The orator no longer considers that he may be called to account for his utterances; he allows himself to be carried by the impulse of the moment, without reflecting on ultimate consequences, and, as his expressions become freer, they acquire an appearance of warmth, of feeling, of inspiration. Not a little of this inspiration is contributed by the audience if they are in a similar condition of increased appreciation.

The view that alcohol increases the intellectual and physical powers of the individual is shown by actual experiments to be erroneous, and based almost entirely upon the subjective condition of the individual, his weakened faculty of judgment and precipitate but faulty or misdirected reactions. The failure of alcohol to produce real stimulation is also attested by common experience. Persons who have to undergo severe exertion, either physical or intellectual, rarely take alcohol before or during their labor, but only when this is finished, and then not for any stimulating, but really for its depressing, effect, for the feeling of comfort and general relaxation which it induces. The continued use of large doses of alcohol diminishes the activity of the individual, and even moderate doses tend to have the same effect.

Another characteristic feature, evidently resulting from this paralysis of the higher functions, is the *loss of the power to control moods*. There may be causeless merriment or sadness, friendliness or the opposite. It is proverbial how this abolishes self-control: "There is truth in wine." On the other hand, habits of self-control, where they have been cultivated, persist to some extent even in intoxication.

Efficiency Tests.—Independent investigations on typewriting, target pricking and rifle practice have shown uniformly that effective doses of alcohol lower efficiency by decreasing accuracy. This becomes especially conspicuous when the work is rapid, and when it requires close and continuous attention. Speed may not be reduced. The deleterious effects are least marked in tasks that are so familiar, or so easy and simple, so "semi-mechanical," that they do not require much attention. The details differ, especially in degree, for different tests and the conditions under which they are made, as well as for different individuals, and whether or not they are accustomed to alcohol and have learned to know their reactions and to allow for them. Most observers conclude that 30 Gm. of alcohol or even less have definite effects on performance and behavior.

After 10 Gm. of alcohol, no change could be demonstrated in the "higher mental abilities" in fifty subjects; 20 Gm. gave doubtful results (B. B. Cattell, 1930). Doses of 20 to 40 Gm. of alcohol practically double the errors in close work, and the effect with this dose lasts about two hours. With some individuals, 10 Gm. may produce the result; habitual drinkers are more resistant. The concentration in which the alcohol is given does not materially influence the response; but the effect is less if the alcohol is taken with or just after meals, for then it would be more slowly absorbed (Vernon and Greenwold, 1919; W. R. Miles, 1924). Heise, 1934, reported that 30 cc. of whisky, equivalent to 15 cc. of alcohol, increases speed but with carelessness, want of self-control and poor judgment.

The University of Chicago investigation of beer (1934) illustrates the difference in individuals. It included thirty-six subjects of various antecedents, tested for equilibrium (Romberg test), pricking, response to signals, and red and green light. The unit of dosage was the customary 350 cc. "bottle" of 3.2 per cent beer, equivalent to 13.65 cc. of alcohol. Two bottles consumed in fifteen minutes had no apparent effect; with four bottles in thirty minutes five tests in sixty-nine showed definite impairment of motor control; eight to fourteen bottles (109 to 190 cc. of alcohol) in three and a half hours showed consistently poor performance, except for visual reaction time. Of twelve subjects, eleven showed definite changes in behavior, and eight vomited.

Experimental Analysis of the Psychic Effects of Alcohol.—Jellinek and McFarland, 1940, analyzed 170 published papers on psychologic experiments with alcohol and concluded that the effects are purely depressant. Dodge and Benedict, 1915, who aimed to use the simplest methods of a given kind, found that moderate doses depress all kinds of neural processes, motor as well as sensory. The diminished efficiency is most conspicuous in the simpler and unconscious reflex processes, *i. e.*, those that are most independent of the will; for a normal individual even when somewhat alcoholized attempts automatically to compensate for diminished efficiency by greater effort. This in turn is likely to lead to more errors; for the extra effort is often ill directed, since alcohol diminishes caution and inhibitions.

Dosage, Time and Subjects.—Dodge and Benedict employed doses of 30 and 45 cc. of alcohol, diluted to 20 per cent. The depression reached its maximum in one to two hours; recovery started within three hours. The responses were essentially similar for abstainers and reformed drinkers.

Quantitative Response.—The results may be arranged in progressive order from those showing the greatest, to those of the least effects. *Reflexes:* knee jerk and lid reflex: latent period increased by 10 and 7 per cent. Muscle shortening diminished by 46 and 19 per cent. *Sensory Thresholds to Electric Stimulation:* raised by 14 per cent. *Motor Coordinations:* speed of eye movements and of reciprocal finger movements: diminished by 14 and 9 per cent *Elaborated Reactions:* reaction time of eye and speech organs; latent period increased by 5 and 3 per cent. *Memory:* no change.

Kraepelin, 1892, also concluded that alcohol is purely depressant to sensory or intellectual processes; but he believed that the generation of motor impulses is first stimulated, and only later depressed. In the light of more recent work, this "stimulation" of motor processes is apparently an erroneous interpretation; but this does not destroy the value of the actual data of the extensive studies of Kraepelin; namely, that the "stimulant" stage of alcohol favors mechanical performances—the "simpler reactions" of memorizing, mechanical reading, repetition, at the expense of the more intellectual processes—association, arithmetical and so forth. It favors motor impulsiveness, but produces intellectual dulness and silliness, lowers thought, judgment, resistance to temptation, and thus leads to further abuse. The euphoria probably depends on the deceptive feeling of facilitation and capability.

Psychic Depression.—With doses of 30 to 45 Gm. of alcohol, this lasts thirty to forty-five minutes; with 60 Gm., one to two hours. The phenomena are somewhat analogous to those of fatigue. In both, mechanical associations predominate. However, the lighter grades of alcohol "fatigue" disappear with exercise, while genuine fatigue is relieved only by rest.

Electroencephalogram changes of alcoholic intoxication are reported by G. L. Engel and Rosenbaum, 1945.

Motor Processes.—The facilitation begins at once and lasts at most twenty to thirty minutes; less with larger doses. It is followed by depression even with the small doses of 7.5 Gm. With 45 to 60 Gm., the initial facilitation is seen only exceptionally. The results depend somewhat on circumstances; in excitement, even large doses produce facilitation; and in fatigue, small doses may depress. The more mechanical the function, the more conspicuous is the facilitation. The force measured by the dynamometer is not increased, so that the rate rather than the force of motor impulses is favored. There is evidence that the muscular contraction proper is not quickened, but that the motor impulses are started more easily.

Perception of sensory impressions is impaired for hours, even by 7.5 cc. of alcohol (Kraepelin, 1916).

The *reflexes* from the frog's skin are depressed, even with the smallest effective doses (Hyde and pupils, 1913), before there are any gross symptoms.

Color Vision.—H. Schuly, 1916, found that small doses of alcohol increase the acuteness of vision, both for red and green. Large doses diminish it.

Alcohol on Muscular Work.—Ergographic experiments of Lombard, 1892, on man showed that the muscular force in voluntary contractions is not increased; but the appreciation of fatigue is lessened (Joteyko, 1904; Foerster, 1912), so that the total work may be increased. When a finger is tetanized, by electric stimulation, the total work is rather decreased (Lombard); the favorable effect must therefore be at least partly central (facilitation of cerebral motor processes). The voluntary response is modified by the previous state of the muscles as well as by the dosage of alcohol. Myers, 1912, reports no effects from 5 to 20 cc.; 30 to 40 cc. gave irregular results, most commonly a primary increase and secondary decrease of the work. The increase is seen only when the muscle is not too much exhausted, but it is favored by moderate fatigue. The depression of the larger dose is purely central. On *frog's muscle*, minute quantities have no effect; moderate doses were said to exert a favorable action on all the features of muscular activity; larger quantities are unfavorable (Lee and Salant, 1902). Crider and Robinson, 1916, attributed the reported favorable effect to experimental error. The *effects on invertebrates and lower vertebrates* were studied by Fuehner, 1912.

Alcohol and Automobile Accidents.—Various studies show marked increase of frequency and seriousness of automobile accidents with slight degrees of alcoholism, increasing with the amount. Effects of alcohol which are not considered as drunkenness in the ordinary sense, and which may not be apparent to the casual observer and even to some efficiency tests, are dangerous in driving automobiles. Diminished acuity of peripheral vision (R. Pickard), poor muscular control, slowed reaction time, impaired self-control and poor judgment when confronted with unexpected situations; and especially self-complacency, so that the driver does not compensate for his impairments; and above all, mania for speed and recklessness in taking chances, constitute a vicious circle that leads to disaster. This is shown by tests in the laboratory and on the road (H. A. Heise, 1934), and especially by the investigation of automobile accidents. It appears that practically any amount of alcohol increases the liability to automobile accidents, incidentally also on the part of pedestrians; and that the increase becomes alarming above 0.5 per thousand blood concentration, equivalent to 50 cc. of alcohol, or 4 ounces of whisky, or two to four bottles of beer.

Holcomb, 1938, who studied 270 drivers involved in motor accidents, and 1760 drivers picked at random near Chicago, found alcohol present in four times higher ratio in the accident group (47 per cent) than in the random group (12 per cent). Up to 0.5 to 0.6 per thousand concentration of alcohol in the blood (the maximum allowed to drivers in Norway), the percentage of accidents was about the same as without alcohol; but above this concentration, the ratio of accidents rose rapidly, so that with 1 per thousand it was four to six times that without alcohol; with 1.3 per thousand it was ten times, and with 1.5 per thousand of alcohol (The National Safety Council's "conclusive evidence" of drunkenness) it was twenty-five times as frequent as in drivers without alcohol. (The doses that give these concentrations are discussed below.) Confirmation of these conclusions by another approach is furnished in the data of Sachsenberg, 1938, from Germany, who found the percentage of "unsafe" drivers, incapacitated so as to be more reckless than 90 per cent of nonalcoholic drivers, to increase from 20 per cent at 0.2 per thousand blood concentration, to 40 per cent at 0.4; 49 per cent at 0.5; 66 per cent at 0.7; 75 per cent at 0.8; 87.5 per cent at 1.0; 90 per cent at 1.1; and 100 per cent at 1.4 per thousand. Heise, 1934, found decrease of efficiency even after an ounce (30 cc.) of whisky, with blood concentration not above 0.2 per thousand, although the ordinary psychomotor tests of alcohol were not positive till 150 cc. of whisky had been taken.

Use of Alcohol as Stimulant.—Although the "stimulant" doses do not increase intellectual efficiency, they could be employed for facilitating motor functions of short duration; not so much to increase their force, but for overcoming inhibition of hesitancy; to promote decision or resolution, *f. i.*, in speaking, in psychic dreads, and so forth. It would be unfavorable to attention, watchfulness or accurate judgment. The stimulant dose should generally not be more than 15 to 20 Gm. of alcohol; or if a longer effect is needed, 5 to 8 Gm. in twenty-minute intervals.

The *use of alcohol in convalescence and debility as an "analeptic," "restorative"* or *"stimulant"* is supported by long experience. The feeling of well-being caused by it, the sense of capability, the removal of worry, the enjoyment in the act of taking it, the rest and sleep induced by its narcotic action, its food value and its beneficial effects upon digestion, concur in its action. To this may be added its slight effects upon the vascular system—the altered distribution of blood, the diminished resistance to the heart—which may be of benefit in some cases. For these purposes, the alcohol should be taken well diluted, as light wines or beers.

The contraindications to alcohol may be resummarized as: danger of habit; states of excitement; sthenic stage of fevers; irritation of the alimentary or genito-urinary tract.

Use of Alcohol in Depressed Psychical States.—In hypochondria, melancholia, neuralgia and other obscure nervous diseases, alcohol relieves the patient by its mild narcotic and euphoristic action, but the temporary relief is generally obtained at the expense of a permanent alcohol habit, and is therefore not to be advised. *In catatonic syndromes,* alcohol may interrupt the catatonic stupor, producing temporary and sometimes lasting cessation of the mutism, torpor and negativism (Kantorovich and Constantinovich, 1935).

Use of Alcohol as a Hypnotic.—Alcohol, especially in the form of beer, taken at night and in the absence of excitement, is a fairly efficient hypnotic; but its usefulness is limited by the danger of chronic alcoholism. The hypnotic dosage corresponds to 45 to 60 Gm. of alcohol.

Alcohol analgesia has been used since antiquity to confer "Dutch courage." The heat-pain method shows that it produces indifference to perceived pain. The maximal analgesia, amounting to 45 per cent increase of threshold, is produced by 30 cc. of alcohol in about fifteen minutes, and lasts about two and a half hours; longer with larger doses (H. G. Wolff *et al.*, 1942).

Mullin and Luckhardt, 1934, confirmed with the Frey bristle technic that 60 to 75 cc. of alcohol, administered by mouth as 20 per cent dilution, distinctly decrease pain sensitivity for two or three hours. Sensations other than pain are not affected by ordinary doses (Wikler *et al.*, 1945).

General anesthesia by intravenous injection of alcohol is described by E. V. Verkovskaya, 1945: 2 to 2.5 cc. of alcohol per Kg. of body weight, diluted with twice its volume of 5 per cent dextrose solution, is administered by drip injection in ten to fifteen minutes (the fatal dose ies about 7.7 cc. per Kg.). Sleep sets in with about 1 cc. of alcohol, and lasts two to five hours. The patient awakens irrational and requires watching. Vomiting occurs in 6 per cent. Intravenous alcohol anesthesia for animals is described by Nitzescu, 1930.

Spinal reflexes are first augmented, then depressed, in spinal cats and in fish. Other alcohols and ether act similarly; the stimulation is doubtful with chloroform (Fuehner, 1926).

Respiration.—"Stimulant" doses of alcohol may increase the rate and depth of the respirations, by reflex and central stimulation. The response, however, is variable and generally small. With narcotic doses, the respiratory center is depressed. The *hypodermic injection* of 50 per cent alcohol (or of whisky or brandy) produces considerable temporary increase of respiration, by reflex irritation. This occurs also under morphine (Hanzlik, 1913).

In Higgins' experiments (1917) on *man*, 30 to 44 cc. of alcohol taken diluted produced little change in the rate or type of respiration (unless there was excitement). The threshold to CO_2 was sometimes lowered. The minute volume was generally diminished, by decreased CO_2 production. The bronchioles were generally unaffected; rarely dilated. The respiratory stimulation is especially large in fatigue. Wendelstadt, 1899, obtained similar results in man. The increased respiration is partly due to the general excitement and partly to reflexes from the local irritation (Jacquet, 1895). Some increase occurs even in sleep, so that the factors of environment are not essential. Nor can it be affirmed that it is due solely to reflex irritation, for other irritants do not produce an equivalent effect (Binz, 1903). Moreover, an immediate increase of respiration occurs if alcohol is injected into the brain through the carotid artery (Wilmanns, 1897). With *unanesthetized animals*, slow intravenous injection produced only slight respiratory stimulation, even when the injections were repeated beyond the excitement stage (Hyatt and Jensen, 1918). With a more perfect separate *perfusion* of the brain and medulla, Hooker, 1917, also found that the addition of 0.025 to 0.1 per cent of alcohol (corresponding to clinical concentrations) produces pure stimulation of the respiration. With 0.2 per cent, the stimulation was transitory, and was followed by prolonged inhibition. This would correspond to coma. It is therefore certain that the respiratory center is stimulated directly. In *cats*, Pilcher, 1912, found the rate usually increased by all except fatal doses. In *decerebrated cats*, doses of 0.5 to 5 cc. per Kg., dilute or concentrated, caused no change in the respiration (Lieb, 1915). With *decerebrate* and *vagotomized rabbits*, alcohol (10 cc. of 5 per cent per Kg.), heptyl alcohol and ether stimulate the respiratory center; chloroform does not (Blume, 1928).

The **effects on the circulation** are rather minor and inconstant, largely secondary to other actions, varying not only with the dose and concentration and mode of administration, but also with the condition of the individual. *Small therapeutic doses* (in man, to perhaps 5 to 25 cc. of absolute alcohol, diluted to at least 25 per cent) produce generally (but not always) an insignificant quickening of the pulse rate, due mainly to excitement. There is no evidence of direct cardiac stimulation (A. Grollman, 1942). The cutaneous vessels are dilated, and the splanchnic vessels are somewhat constricted, leading to a rise of the systolic blood pressure and a fall of the diastolic pressure. The mean aortic pressure rises slightly in most cases, but not always. The actions, taken together, alter the distribution of the blood, so that more is contained in the surface vessels and in the arteries, and less in the splanchnic veins. The amplitude and force of the pulse, the "mass movement" of the blood, the output of the heart, and the efficiency of the circulation in general are improved. Cardiac dilatation may be decreased. The actions reach their maximum in about half an hour, and disappear in an hour or two.

In men not accustomed to alcohol, even 10 cc. provoke a psychic response with transient rise of pulse rate, blood pressure, cardiac output and rise in the oxygen of the venous blood. *In moderate drinkers*, 30 cc. does not produce any demonstrable effects, in the absence of excitement. With 35 cc. or more, there are slight changes of pulse rate and appreciable increase of blood pressure and cardiac output (Grollman, 1930).

Somewhat larger doses (45 to 90 cc. of alcohol for man, diluted) produce at first the same effects, followed in an hour or less by decreased amplitude and force of the pulse, with progressive fall of the systolic pressure, and unaltered or rising diastolic pressure. If the alcohol is taken in more concentrated form on an empty stomach, this stage may occur at once, without the preliminary improvement of the pulse. The fall of the pressure is attributable to splanchnic dilatation, replacing the constriction of the first stage. The action is therefore comparable to that of the nitrites. The effects reach their maximum in one to one and one-half hours, and last one-half to one hour.

Toxic doses depress the vasomotor center, so that the blood pressure falls severely. The heart rate may be slowed through central vagus stimulation, or through the depressant action of the coma; or it may be quickened by the fall of blood pressure. It fails finally from anoxia, consequent on respiratory depression; the alcohol concentration of the blood is not sufficient to produce serious direct cardiac injury (H. W. Haggard *et al.*, 1941).

The hypodermic injection of whisky, like that of other volatile irritants, often produces a slight and transient rise of blood pressure (Lieb and Herrick, 1917).

Heart Rate.—The effect is greatly modified by the condition of the individual. In man, the rate is generally increased, mainly by the psychic and reflex actions (Dixon, 1907); the increase is often absent, especially if the patient keeps quiet (Zimmermann, 1896; Jacquet, 1891; Dixon). With larger doses quickening is the rule (John, 1918; Higgins, 1917), presumably to offset the falling blood pressure. Animals give similar inconstant results (Pilcher, 1912). The intravenous injection into nonanesthetized animals generally causes some slowing (Brooks, 1910).

General Blood Pressure.—*In man*, Lieb, 1915, observed practically no effect from diluted whisky (usually 5 to 10 cc.). When given concentrated, this dosage usually produced a slight reflex rise (about   mm.) of the systolic and diastolic pressure, returning to normal in less than one-half hour. The return of the diastolic pressure is somewhat slower, so that the pulse pressure is decreased. These effects are entirely reflex, and are most pronounced when the reflexes are hyperactive; least in apathetic patients and toxemias. Moderate users are more susceptible to them than are drinkers. With larger doses John, 1908, found a progressive fall of systolic pressure, with unchanged or rising diastolic pressure. In *unanesthetized animals* the oral administration produces a slight rise, lasting five to ten minutes; administration through a gastric fistula had no effect. Rapid intravenous injection causes the sharp drop, common to many drugs, followed by rapid recovery. Slow intravenous injection produces no marked change with doses of 0.5 to 5 cc. per Kg. (Brooks, 1910; Lieb, 1915; Hyatt, 1920).

Blood Flow.—Alcoholic beverages of the strength of wine, administered to normal men in moderate doses, produce a brief preliminary decrease, followed by a more lasting increase, of the blood flow in the hand. Both effects are vascular. Alcohol also favors vasodilator reflexes; *f. i.*, the contralateral heat reflex (G. N. Stewart, 1915). Hanzlik and Collins, 1913, found the circulation time in intestinal vessels distinctly slowed by relatively small doses of alcohol, intravenously, even when the carotid pressure was unchanged.

Vasomotor Changes.—Moderate doses of alcohol dilate the *skin capillaries* and lower the *vein pressure*, without change in the arterial pressure (McDowall, 1925). (Large doses increase the vein pressure; Capps and Matthews, 1913.) Since the blood pressure does not fall in the early stages, it is evident that this dilatation of the surface vessels is compensated, either by the constriction of other vascular areas or by increased output of the heart. Both factors appear to contribute to the result, according to circumstances. A brief turgor of the *posterior urethra* seems to follow the swallowing of a moderate quantity of alcohol. *Splanchnic vasoconstriction* in the early stage was demonstrated by Dixon, 1907, who found that the volume of the intestine decreases while the blood pressure rises.

General vasodilatation in the more advanced stages of the action is shown by the fact that the blood pressure is practically not increased, notwithstanding considerable increase of the output of the heart, as measured by the stromuhr (Hemmeter, 1889; Wood and Hoyt, 1905) or by the cardiometer (Dixon). If the vasomotor center is excluded by section, the injection of alcohol causes a more marked rise of pressure (Kochmann; Wood and Hoyt), showing that the vasodilator action of alcohol must be central. Porter and Turner, 1915, found that alcohol may suspend *vasomotor reflexes* even when the general level of the blood pressure is not altered. *Direct actions on vessels* appear to be insignificant. On perfusion, Dixon found in mammals slight dilatation with 0.1 to 0.2 per cent; higher concentrations gave constriction. Perfusion of the frog showed moderate constriction. In surviving arterial rings, Cow, 1911, found slight response: transient constriction followed by dilatation. Plumier, 1905, believed that alcohol has a peripheral constrictor effect.

Improved Nutrition of the Heart.—The *increased output of the heart in situ* is attested by the stromuhr, cardiometer, rise of pressure after destruction of the vasomotor center, and so forth. Since this improvement is not usually noted in excised hearts, it cannot be due to a direct action of alcohol on the cardiac muscle. Kochmann, 1905, attributed it to improvement of the coronary circulation by the general vascular changes. Peters, Rea and Grossman, 1936, found with Starling heart-lung preparation of dogs that alcohol in the concentration of drunkenness decreased the oxygen consumption, with decreased external efficiency.

Isolated Mammalian Heart.—Concentrations below 0.05 per cent generally have no effect. Occasionally there are indications either of depression or of stimulation; the latter especially if the heart has been exhausted (Dixon, 1907). Between 0.05 and 0.5 per cent, some depression becomes evident. This is first seen as increased volume, in systole and diastole, which progresses with the dosage, and develops into diminished output, rise of venous and pulmonary pressure, slight slowing and some tendency to arrhythmia. With 2 per cent, the heart is severely damaged, especially the auricles. Four to 5 per cent arrests the heart in diastole; the auricles stop before the ventricle. If the alcohol is removed, the heart recovers rapidly, even from severe depression (Sulzer, 1924; Kochmann, 1904; O. Loeb, 1905; Barry, 1915; Burridge, 1917; Lieb, 1917). The *coronary vessels* are said to be constricted, and the coronary flow diminished, by 0.1 to 0.2 per cent of alcohol (Sulzer, 1924).

The concentration of alcohol in the blood of living animals is 0.12 per cent in "slight confusion," and 0.7 per cent in deep narcosis. It is therefore improbable that the direct cardiac effects of alcohol play more than a minor part in either the therapeutic or toxic phenomena.

The *frog's heart* is stimulated by small, and depressed by higher, concentrations (Wood and Hoyt, 1905); according to others, even the smaller doses are depressant (Dreser, 1887; Toyoshima, 1928).

Turtle Heart.—The concentration required to reduce the height of contraction to one-half was studied for various alcohols by Vernon, 1910.

Pressure in Pulmonary Artery.—Dixon, 1907, and Wood, 1911, found this slightly increased, even when the carotid pressure is unchanged. Cloetta and Anderes, 1914, found the effect on the pulmonary vessels inconstant; generally dilatation, rarely constriction.

Cerebral Circulation.—Hirschfelder, 1915, described dilatation of the vessels of the pia mater and retina. Berezin, 1916, also observed dilatation.

Hemolytic Action—Alcohol added in sufficient concentration directly to blood causes hemolysis (C. H. Schulz, 1841). This concentration is not reached in living animals, but the resistance to laking agents is noticeably lowered (Fillinger, 1912). Continued administration increases the resistance of the corpuscles (Orban, 1913). If the relative hemolytic effect of different alcohols is compared, it is found to be proportional to their effect on surface tension, rather than to their lipoid solvent action (Fuehner, 1912). J. N. Schultz, 1912, investigated the influence of various substances (including sera in different diseases) on the alcohol hemolysis.

Blood viscosity is somewhat increased by the administration or inhalation of alcohol or methyl alcohol (Burton-Opitz, 1904, 1914).

Cerebrospinal fluid formation is increased by alcohol (Tajitsu, 1929). The *pressure* of the cerebrospinal fluid is not changed by alcohol unless it is lowered consequent on fall of systemic blood pressure (Bedford, 1946).

Use of Alcohol in Collapse.—Alcohol is used as a quickly acting ("diffusible") stimulant in sudden circulatory collapse, syncope, exhaustion, hemorrhage, traumatic shock, snake venom, strychnine, aconite, veratrum poisoning, and so on. The main element in this action is the reflex stimulation, increasing the pulse rate, the blood pressure and the respiration. The stimulation is prone to fail in the severer grades of hemorrhage and shock (Lieb and Herrick, 1917). The narcotic action may be useful. The subsequent vasodilatation is not sufficiently pronounced to have practical significance. The reflex action being brief, alcohol acts mainly as a temporary emergency remedy, to tide the patient over the immediate dangers. To secure these reflex effects, 25 cc. of whisky or brandy should be given undiluted, preferably hot, repeated every ten to fifteen minutes, according to effect. Similar reflex stimulation may be secured by *other diffusible stimulants:* ether, aromatic oils, camphor or ammonia. These may be administered by mouth (Spiritus Aetheris; Spiritus Camphorae; Spiritus Ammoniae Aromatics), or by smelling (aromatic ammonia, smelling salts).

Cardiac Disease.—Alcohol may be useful for temporary conditions, such as acute *myocardial insufficiency.* In *chronic lesions,* small doses may be valuable to lessen the worries of the patient, especially if he has been accustomed to its use. The vasodilator effect may be useful in *angina pectoris,* but it is inferior to the nitrites. Alcohol does not influence *pulmonary hemorrhage* (E. Frey, 1909).

Use in Exhausting Fevers (Typhoid, Pneumonia, and the like).—The discriminating employment of alcohol may be useful in these conditions; its indiscriminate use would do more harm than good.

The beneficial effects are probably mainly nutrient, owing to the *food value of the alcohol* and to the stimulation of the digestion and absorption of other foods. This not only conserves the general nutrition of the patient, but *increases the output of the exhausted heart.* The pulse becomes stronger and more regular. The altered distribution of the blood by the mildest degrees of alcohol action would also be beneficial: The *dilatation of the cutaneous vessels* removes the blood from the atonic and therefore congested internal organs, and lessens the venous distention of the heart. It would tend to lower the temperature, although the antipyretic effect is but small. The narcotic action of alcohol is useful by quieting the febrile excitement, thus reducing the demands on the strength of the patient. On the other hand, if the action of the alcohol proceeds to the point of inducing splanchnic dilatation and lowering blood pressure, it will exaggerate the serious circulatory abnormalities of fever. Again, in the acute, stimulant stages of the "sthenic" fevers, alcohol is likely to increase the circulatory excitement, and should be avoided. The individual observations on each patient can alone guide its employment: The dose may be increased or maintained so long as it improves the prominent symptoms, quiets the patient, regulates and strengthens the pulse, and lowers the temperature. When it ceases to have these effects—particularly when the pulse becomes "excited," or when the odor of alcohol remains on the breath—it should be diminished or stopped. The amount should be governed by the previous habits of the patient; but astonishingly large quantities can often be given to fever patients without producing inebriation even if they are unaccustomed to its use; the febrile organism probably oxidizes the alcohol more rapidly. Ordinarily, one may begin with ½ to 2 tablespoonfuls of brandy in half a glass of milk, every three hours, increasing the frequency as needed.

Temperature.—The ingestion of alcohol causes a sensation of warmth, due to the increased blood flow to the temperature nerves of the stomach and skin. This sensation is deceptive, for increased blood flow to the surface and the *diaphoresis* increase the heat loss, so that the internal temperature tends to fall. With small doses this tendency may be overcome by the increased movements of the patient; but with larger doses the heat loss becomes pronounced (Pilcher, 1912), and is exaggerated by the depressant action on the temperature-regulating centers, impairing the compensatory heat production. The fall of temperature is especially great if the surrounding atmosphere is cold, and also if the heat dissipation was previously low, as in fevers.

Use of Alcohol in Chills and Exposures.—It is evident that this would be detrimental *during* exposure to cold; the temporary relief and feeling of warmth is obtained at the expense of an increased loss of heat, and consequently diminished power of resistance. But if taken *after* the exposure, the dilatation of the cutaneous vessels favors the absorption of external heat, and also prevents the tendency to congestion of internal organs, and thereby the tendency to "catch cold." Another effect may be important: Constriction of the cutaneous vessels, such as is produced by chilling, leads to reflex constriction of the vessels of certain internal surfaces and organs, especially the respiratory tract and perhaps the kidneys, so that these are rendered less resistant to infection and injury. Cutaneous vasodilatation by alcohol, the nitrites or by counterirritation may prevent or arrest the damage.

The diuretic action of alcohol is parallel to its concentration in the blood (M. G. Eggleton, 1922), aided by the ingestion of fluid when the drink is beer; the other ingredients of alcoholic beverages are not important in this respect (H. W. Haggard *et al.*, 1941), with the exception of the juniper oil of gin.

John, 1908, found the average quantity of urine in four to six hours after taking 1½ liters of water to be 1500 cc.; with 1½ liters of 3 per cent alcohol, he averaged 1800 cc.; with the same quantity of 6 per cent alcohol he averaged 2000 cc. of urine. Alcohol irritates the urinary passages or perhaps rather causes a reflex turgor of the posterior urethra (and is therefore *contraindicated in cystitis and urethritis*); this may increase the desire to micturate, and may make the diuretic effect appear greater than it really is. Dogs fail to show more than the water diuresis, with oral administration of any dosage of alcohol (Januskiewicz, 1911). (Intravenous injection would arrest the urine flow, as do other hypotonic solutions.)

Local Actions of Alcohol.—Concentrated alcohol "hardens" tissues by abstracting their water and precipitating the proteins. It is therefore irritant and astringent. The effect is proportional to the concentration.

Applied to the skin, it causes some redness and smarting, followed by slight anesthesia. It is employed as a *mild rubefacient* and counterirritant in sprains and other minor pains. It may be applied in 10 to 70 per cent concentration, by friction or embrocation. It is often combined with other mild irritants, as in Soap Liniment, Camphor Spirit, "Witch-hazel Water" and Arnica Tincture. If the alcohol is sponged on the skin and permitted to evaporate, it produces a *cooling effect.* This is utilized in *fever,* and in excessive perspiration ("night sweats" of phthisis). The cleansing and hardening of the skin are also useful in this connection to prevent the development of *bed sores.* The astringent and stimulant action promotes the healing of *ulcers* (25 to 50 per cent).

On *mucous membranes,* the local action produces hyperemia or inflammation according to the concentration. The diuretic action of alcohol indicates that it irritates the renal cells.

Cell Division of Epithelium of Frog Skin.—Weak solutions produce marked increase of mitosis; a stronger (0.8 M) concentration causes irregular and incomplete metaphase; 1.2 to 1.5 M result in gelatinization of the cells. Methyl and propyl alcohol produce qualitatively similar effects (Aisenberg, 1936).

Subcutaneous injections of alcohol in concentrations above 50 per cent are painful and may cause ulceration; especial care should be used not to inject it near a nerve.

Intraneural injections of alcohol were introduced by Schoesser for the relief of neuralgia and spasms. They are generally effective, but are frequently followed by toxic degeneration of the nerve. They should therefore be avoided for motor or mixed nerves (sciatica), and find their best field in trigeminal neuralgia, as a substitute for the extirpation of the gasserian ganglion (Fischler, 1907), which they have largely superseded. Their effect is not permanent, nor are they entirely free from risk; but they have a field of usefulness. Cadwallader, 1915, studied the results of various concentrations: 80 per cent alcohol produces immediate and complete paralysis followed by absolute histologic degeneration. The paral, ysis may persist for one to three years, or until regeneration is complete; in scar formation there may be no regeneration. Fifty per cent causes less severe paralysis and degeneration; 25 per cent has but little effect in either respect.

Bactericidal Action of Alcohol.—Nonsporing bacteria on dry surfaces are killed by short exposure to alcohol of 50 to 90 per cent; 95 per cent is less effective, 100 per cent notably less. The normal moisture of the skin dilutes the concentrated alcohol so that it is generally effective (G. T. L. Archer, 1945), but 70 per cent (by weight) is preferred for skin sterilization. Friction increases the effectiveness by insuring better contact (A. Beyer, 1911; P. B. Price, 1939).

When tested by dropping bits of a rat's tail into the solution, 70 per cent ethyl alcohol sterilized in five minutes, 50 per cent propyl alcohol in one minute. The propyl alcohol is therefore more effective. The following failed to disinfect in five minutes: phenol, 2 per cent; mercuric chloride, 0.1 per cent; formaldehyde, 4 per cent; Dakin's solution; ether; acetone (Christiansen, 1918).

The **influence of alcohol on digestion** varies with the quantity and concentration, with the state of the digestive functions, with the habits of the individual, and probably also with the flavor and extractives of the beverage. In general, moderate doses act as "condiment" or stimulant to digestion. In this the flavor and the hyperemia cooperate to increase the appetite, the flow of digestive juices, the movements of the stomach, and absorption. The action of ferments is also accelerated. *Small quantities* of alcohol, taken with meals, therefore tend to have a favorable action on digestion. If digestion is perfectly normal, these effects are superfluous; the utilization of food and the total time of digestion are scarcely influenced. In pathological conditions, in depressive emotional states, and perhaps in overeating, the effects may be beneficial. With oral administration, in man as well as in animals, the favorable effect obtains with concentrations up to 10 per cent; with 10 to 20 per cent, the mucus is increased, as well as the juice. Above 20 per cent, the mucus is further increased, but the secretion is decreased. *Large quantities* of alcohol, especially when in concentrated form or in the empty stomach, produce irritation which surpasses the physiologic limit and interferes with the functions. This is seen most markedly in the habitual use, when the inflammatory changes become chronic.

Use of Alcohol in Indigestion.—Alcohol, in the form of wine or diluted spirits, taken with meals, is clinically of value in some forms, and harmful in others. It would be useful as a "counterirritant" in functional colic and gastralgia, and harmful in acute gastritis. The euphoristic and calmative actions tend to prevent and remove the unfavorable inhibitory effects of depressed or harassed and irritable mental conditions; so that alcohol may be valuable in the course of or convalescence from fevers or exhausting illness, phthisis, and so forth, and it may be a useful adjustant in nervous dyspepsia. Sometimes it is harmful by increasing the hyperchlorhydria. Champagne is also used as an *antemetic*. Its action depends perhaps more on the carbon dioxide and cold and on the psychical effect, than on direct actions of the alcohol.

Normal Human Gastric Functions.—These were studied by Beams and Barlow, 1936, in a number of normal men, by analysis of gastric contents and roentgenoscopy. Fifty cc. of alcohol (500 cc. of 10 per cent) produced marked increase in gastric tonus and peristalsis, but with lengthened emptying time. With the therapeutic dose of 15 cc. (as 500 cc. of 3 per cent), the effects were slight, but in the same direction. With the same dose, as 50 cc. of 30 per cent, there was marked increase of mucus and acid secretion, the free acid more than the total. With 3.5 cc. (50 cc. of 7 per cent), the acid was increased similarly, but the mucus was not. Concentrations of 5 to 10 per cent in man slightly increase the gastric peristalsis and tonus, and somewhat prolong the time of emptying (von Friedrich and Bokor, 1934). *Hunger contractions* are inhibited by alcohol, as by many other chemical and mechanical stimuli—food, smoking, chewing, dilute acids or alkalis (Carlson, 1913). Alcohol may, however, render the sensation of hunger more intense (W. W. Scott *et al.*, 1938).

Excised Intestine of Rabbit.—The movements are mainly depressed by monovalent alcohols; very dilute solutions produce a primary stimulation (Kuno, 1914).

Secretion of Saliva.—The presence of alcohol, strong or dilute, in the mouth increases reflexly the amount and the solids of the saliva, as do many other substances (acetic acid, ether, and so on). This increased secretion does not take place if the alcohol is introduced directly into the stomach through a fistula or if it is given subcutaneously.

Secretion of Gastric Juice.—The oral administration of 50 cc. of 7 per cent alcohol is used as a clinical *test of gastric secretion* (Bloomfield and Keefer, 1928). The secretogogue action is ordinarily due to peripheral parasympathetic stimulation, for it persists after section of the vagi, but is abolished by atropine. Some increase occurs, however, if the local action of the alcohol on the stomach is excluded, as in the "Pavlov stomach" (Zitowitsch, 1905; Bickel and Elkeles, 1926), or if the alcohol is placed into the intestine (Chittenden) or rectum (Kast, 1906). Dragstedt, Gray *et al.*, 1940, consider the phenomena similar to those evoked by histamine, and suggested that they are produced by the liberation of this substance

Pancreatic Juice.—Gizelt, 1906, claimed that the secretion is stimulated when alcohol is administered by mouth, intestine or subcutaneously, but only if the vagi are intact.

Bile.—Salant, 1906, found that alcohol by mouth (but not intravenously) increases the flow by 50 to 350 per cent; the solids are also increased. Increased bile secretion was confirmed for large doses by Okada, 1915.

Action on Ferments.—Since alcohol is readily absorbed, and no great amount of it reaches the intestine, it can influence only the ferments of the stomach. *In vitro,* 1 to 2 per cent of alcohol increases the rapidity of peptic digestion. Up to 15 per cent causes no perceptible retardation. With 15 to 18 per cent, the digestion is reduced by one-fourth to one-third. With 20 per cent, the digestion is strongly inhibited (Chittenden, Mendel and Jackson, 1898). Beers and wines have a slightly more unfavorable effect on account of the extractive matter contained in them.

Effects on Absorption.—Alcohol increases the absorption of other substances under certain conditions (Riemschneider, 1900, strychnine; Edkins, 1928, dextrose), but not under some other conditions (Ryan, strychnine, 1912). D M. Tennent, 1941, found absorption of dextrose delayed by increasing doses of alcohol. Brequet, 1912, found only a slight effect on the gastric absorption of strychnine, salicylate or iodide. Tschekounow, 1914, observed no increase for saccharose, iodine or NaCl. Hanzlik found the absorption of phenol and iodide diminished by strong alcohol. Alcohol intended as antidote may therefore even increase the toxicity of poisons, if both are taken by the stomach, and this is not evacuated.

The **absorption of alcohol** occurs rapidly, mainly from the small intestine. The unabsorbed alcohol averages about 50 per cent in fifteen minutes after oral ingestion, 1 per cent after three hours (Harger *et al.*, 1937). The rate is practically independent of the quantity.

Nemser, 1907, found that the amount absorbed at each level of the digestive tract depends mainly upon the time during which the fluid naturally sojourns at this level; little of the alcohol is therefore absorbed from the mouth; about a fifth from the stomach; little from the duodenum; the greatest quantity from the jejunum, and the remaining fifth from the ileum. Hanzlik and Collins 1913, studied the *absorption from intestinal loops* in living animals. It was rather better from the colon than from the stomach or small intestines; the length of the loop had little influence. The intestinal wall retains a certain amount of alcohol firmly, thus apparently arresting its absorption. Voeltz, Baudrexel and Dietrich, 1912, found similar phenomena in the absorption of alcohol by the *urinary bladder*, which is fairly extensive (Nicloux and Nowicka, 1913). Absorption from the *skin* is negligible (R. V. Bowers *et al.*, 1942).

Excretion of Alcohol.—Only a small proportion of the ingested alcohol is excreted, by the kidneys and lungs; generally less than 2 per cent, and probably never more than 10 per cent. The remainder is completely oxidized in the tissues. The proportion excreted depends upon the dose and other conditions. It is greater if the respiration is increased as by muscular work, or if the absorption is more rapid, as when the alcohol is taken on an empty stomach (Voeltz *et al.*, 1912).

Channels of Excretion.—This occurs mainly by the kidneys and lungs; a small amount is excreted and reabsorbed from the urinary bladder. Administering 30 to 50 cc. of alcohol in 250 cc. of water, Carpenter and Lee, 1938, found the total excretion in urine and air to be only 0.8 to 1.6 per cent of the ingested amount, with the subject at rest, and 1.1 to 2.1 per cent during muscular work. The pulmonary excretion is fairly constant, between 2 and 4 per cent; that by urine varies between 1½ and 13 per cent, depending largely on the sojourn and reabsorption in the bladder (Nicloux and Nowicka, 1913). Haggard and Greenberg, 1934, found 2.1 to 4.3 per cent excreted by the *kidneys*, depending on the urine output, and about 8 per cent, with rather wide variations, in the *expired air* A negligibly small quantity is excreted by the *stomach* when alcohol is administered by rectum (Lukas, 1930). The *milk* may contain a small amount if large quantities are ingested, but not with ordinary doses (Klingemann; Koldewijn, 1910; Schottmueller and Schumm, 1912). The maximum amount would be too small to affect sucklings (Voeltz, Paechtner, 1913). Lenoble and Daniel, 1917, found that after ordinary alcoholic intoxication, it appears promptly in the *cerebrospinal fluid*, and persists there for an average of ten days. The excretion curve is similar to that of the urine. It is *not* excreted in the sweat or feces (slight traces by intestinal loops, Hanzlik and Collins, 1913). The excretions do not contain an appreciable amount of acetone or other intermediate decomposition products (Masing, 1854).

The Fate of Alcohol in the Tissues; Effect on Metabolism.—Over 90 to 98 per cent of the ingested alcohol disappears in the body, being completely oxidized to carbon dioxide and water (Atwater and Benedict, 1902), probably with acetic acid as an intermediate stage. The quantity oxidized is proportional to its concentration in the blood (Haggard and Greenberg, 1934). When it is taken in fractional doses, a man of 70 Kg. can burn 240 cc. of alcohol in twenty-four hours (British Royal Commission, 1934). By the chemical energy thus liberated (about 7 calories for 1 Gm. of alcohol, or 4 calories for 1 cc. of whisky) alcohol can replace carbohydrates and fats in the diet. Although it is not used directly in muscular work, since this does not increase the rate of its oxidation (Carpenter, Lee and Burdett, 1933; Carpenter and Lee, 1938; Canzanelli, Guild and Rapport 1934; Nyman and Palmlov, 1934), its combustion conserves other energy material. and it is therefore used indirectly. Its utilization is complete and economical, for it does not increase the basal heat production (Le Breton and Schaffer, 1935; Grubbs and Hitchcock, 1938). By its poisonous side action, however, it may at first cause an increased nitrogen excretion in individuals not accustomed to its use; but this action disappears in a few days, and it then *saves nitrogen* like any other food.

When added to an ordinary diet, the CO_2 excretion, the oxygen consumption and the output of heat are not materially changed (Higgins, 1917). The alcohol therefore saves the other constituents of the diet from decomposition, and the body shows a corresponding gain in weight. If it is added to a diet deficient in carbohydrates or fats, the metabolism is the same as if an isodynamic quantity of these foods were added. When alcohol is added to a complete basal diet of rats, these grow more rapidly than the controls, with greater retention of nitrogen and decomposition of fat. In these respects it is about three-fourths as effective as equivalent quantities of sucrose (H. H. Mitchell, 1935). It spares carbohydrates in man even when large amounts of sugar are supplied (Toegel and co-workers, 1913). Alcohol can also be utilized in the form of rectal injections. Carpenter, 1917, found the respiratory quotient (in man) generally lowered in two to three hours after the injection of 25 cc. of alcohol diluted to 5 or 10 per cent (reviews, T. M. Carpenter, 1940; H. H. Mitchell and Curzon, 1940).

Food Value of Alcohol.—While alcohol is a food, in the sense of being a source of energy, other factors must be taken into consideration. The increased nutrition may itself be detrimental to the body, either by preventing the complete combustion of metabolites or by leading to an abnormal deposition of fat; for it decreases markedly the metabolism of fats, and somewhat that of carbohydrates (Carpenter and Lee, 1937). A more potent objection to considering alcohol as a generally useful food lies in its toxic action, especially its psychical effects. Alcohol should therefore be employed as a food only when a sufficient supply of energy cannot be obtained from an ordinary diet; as, for instance, in *digestive disturbances*, or when the demands on the organism are unusually large, as in *fever*. (The food value of alcohol was reviewed by H. H. Mitchell and Curzon, 1940.)

The proverbial *obesity* of persons addicted to the overuse of weak alcoholic liquids (in which the nutrient effect is less obscured by the toxic actions) is a striking illustration that too liberal a nutrition is not necessarily beneficial. That alcohol lessens the oxidation of metabolites is shown by an *increased excretion of uric acid and ammonia* nitrogen at the expense of urea (Paton and Eason, 1901; Mendel and Hilditch, 1910). This points to a modification of the functions of the liver. *Excessive doses* of alcohol are always detrimental to nutrition, lessening both assimilation and disassimilation. The effects resemble those of the anesthetics.

Rate of Oxidation.—Man can oxidize alcohol at the rate of about 10 cc. per hour; dogs about 0.185 cc. per Kg. per hour (Mellanby, 1919); mice about 0.65 mg. per Gm. per hour, about five times the human rate (Nicloux, Le Breton and Doutcheff, 1934). The rate of oxidation in rats increases with the concentration of alcohol in the blood, about 30 per cent for 100 mg. per 100 cc. (M. G. Eggleton, 1940). The oxidation of the alcohol is completed rather slowly; with 2 cc. per Kg., it requires about eighteen hours (Voeltz and Dietrich, 1915). In man, the combustion of 30 cc. requires about eight hours; of 45 cc., twelve hours (Higgins, 1917). The *rate at which alcohol is oxidized is fairly constant for a given individual* (for instance, the amount which must be injected intravenously to maintain a constant concentration level in the blood; Newman and Cutting, 1935). It is not significantly increased by *habituation* (dogs, 6.8 cc. per Kg. daily for thirteen months; Newman and Cutting, 1936); and small doses of alcohol give the same concentration in the blood, brain, liver and kidneys of habituated as of normal rats (Levy, 1938), so that tolerance is not due to increased destruction. The oxidation of alcohol by minced brain through acetaldehyde and acetic acid is effected by a nicotinic acid and riboflavin (J. G. Dewars, 1943).

The *liver* is apparently the chief site of the initial oxidation of alcohol, and insulin is necessary for this function. Excised diabetic liver does not oxidize significant quantities of alcohol, and this ability is restored by insulin injection (B. B. Clark *et al.*, 1939, 1941). The rate, however of alcohol oxidation, as judged by the blood level and urine excretion, is the same in diabetic as in normal subjects (A. E. Koehler *et al.*, 1944). The data as to the influence of *dextrose* and other carbohydrates with and without *insulin* on alcohol oxidation are confusing. Some investigators report that insulin increases the rate of oxidation of alcohol, especially if dextrose is also injected (B. B. Clark *et al.*, 1941), but others find no effect (R. Gregory *et al.*, 1943). The reasons for the contradiction are obscure. Lang and von Schlick, 1936, did not find any material change of the blood alcohol curve after insulin, caffeine or *thyroxin*. Preusse, 1933, and Widmark, 1935, also found that thyroxin treatment had no bearing on the effects or utilization of alcohol, contrary to Riesser and Hadrossek, and to Vollmer, who had claimed that thyroxin, lactate, glucose and methylene blue render mice less susceptible to alcohol. Large doses of *acetanilid* inhibit alcohol oxidation (N. Rakieten, 1942). *Dinitrophenol* increases the oxidation of alcohol by excised tissues. Safe doses do not do so in living animals (Newman and Cutting, 1935), or only slightly (P. L. Ewing, 1940), but the alcohol is more rapidly eliminated by the increase of pulmonary ventilation (Newman and Tainter, 1936). Similarly, increase of *external temperature* is said to lessen its oxidation, and to promote its excretion (thus 96 per cent oxidized at 16° C.; 92 per cent at 26°; Voeltz and Baudrexel, 1913). Hyperpyrexia by shortwave radiothermy does not materially increase its oxidation rate in dogs (P. L. Ewing, 1940). *Pituitrin* and epinephrine had no effect on the utilization (Widmark, 1935).

Acidosis, with decreased CO_2 capacity of the blood by 4 to 5 volumes per cent, results from large doses of alcohol (5 Gm. per Kg.) in dogs. The lactic acid of the blood is increased by 50 per cent, and after twenty-four hours is still 20 per cent above normal (B. B. Clark and Morrissey, 1938).

Effect on Nitrogen Metabolism.—In man, large quantities, corresponding to 96 cc. of 95 per cent alcohol (500 calories), divided into six doses per day, with constant diet, caused no pronounced disturbance in the alimentary utilization of food. These doses spared protein; the partition of the urinary nitrogen was unchanged, except that the *purine excretion*, both endogenous and exogenous, was increased. Larger doses caused a loss of nitrogen and a relative increase of urinary ammonia. Mendel and Hilditch, 1910, investigated the effects of moderate quantities on man and dogs. With smaller doses (40 cc. of rum, three times daily) and in individuals accustomed to its use, Hammett, 1916, found no increase of uric acid. Stehle, 1915, found no increase in the excretion of endogenous uric acid. Winterstein, 1914, claimed that alcohol increases the gas metabolism of the spinal cord of pigs.

The blood sugar level is somewhat raised by therapeutic doses of alcohol (12 to 17 Gm.) in normal individuals, but is lowered in diabetic patients. The effect appears in half an hour and lasts about five hours (Labbe *et al.*, 1927) It is probably not important. In well fed rats, intoxicant doses (3 Gm. per Kg.; but not 1 Gm. per Kg.) produce a marked increase of blood concentration and decrease of liver glycogen; this effect is absent if the liver glycogen has been depleted by fasting (D. M. Tennent, 1941).

Alcohol in Diabetes Mellitus.—Benedict and Förök, 1906, found that the replacement of 50 to 80 Gm. of food fat by isodynamic quantities of alcohol lessened the excretion of sugar, acetone and nitrogen. O. Neubauer, 1906, also reported it as useful. Higgins, Peabody and Fitz, 1916, found that alcohol (100 to 180 cc. of whisky per day) did not prevent acidosis in normal persons on carbohydrate-free diet. Mosenthal and Harrop, 1918, also found that alcohol was unable to replace isodynamic quantities of protein or even fat in conserving a nitrogen balance. Excessive quantities, however, cannot be expected to exert a favorable action, since the toxic effects will predominate.

Distribution of the Ingested Alcohol in the Tissues.—Since alcohol diffuses readily, it is quickly distributed through the fluids and tissues, so that its concentration is soon practically parallel to their water content (Nicloux, 1933), and inverse to their content of solids or lipoids; the oil: water *partition coefficient* of alcohol is 0.03:1 (Lindenberg, 1933). The concentration is therefore about a third lower in the tissues than in the blood, and a seventh higher in the urine than in the blood (Haggard and Greenberg, 1934). It is notably low in bone and in lipoid tissue. With these two exceptions, the concentration in all the tissues, including the brain, is fairly equal, after equilibrium has been established (Harger, Hulpieu and Lamb, 1937). One to one and one-quarter hours after ingestion, the alcohol concentration of most tissues is 70 to 80 per cent of the plasma concentration; that of fat is 10 to 20 per cent (M. G. Eggleton, 1940). The concentration of the alveolar air is also in equilibrium with that of the blood.

Because of the uniform distribution, *the concentration of alcohol in the tissues* may be deduced fairly closely by dividing the total quantity in the body by the body weight, with some deduction for bone and fat (Mellanby, 1919); the quantity in the body corresponds to the total amount absorbed, less that which has been destroyed or eliminated. The relation of absorption to destruction is determined chiefly by the dose and the time.

Vollmering, 1912, found that soon after absorption the ratio was blood > liver > muscle > brain. Later, the brain contained the most. Adipose tissue was slow to take it up, but retained it longer. Voeltz and Dietrich, 1912, found 3 to 12 per cent still present in the body fifteen hours after doses of 2 cc. per Kg.; 2 to 4 per cent had been excreted by the respiration, 0.4 to 4 per cent by the urine, and 90 per cent had been oxidized. *Quantitative tests* for alcohol in tissues are described by Gettler and Siegel, 1937, Am. J. Clin. Path., *7:* 85; a simplification of Widmark's (1930) test for blood, and so forth, by Abels, 1936, J.A.M.A., *109:* 294. The method of Nicloux, 1931, determines 0.1 mg. with a limit of error of 5 per cent. The specificity of these tests is discussed by Heise, 1934, and Tiffeneau, 1933. They depend on the reduction of bichromate and could therefore be vitiated by other reducing substances, but none such are likely to be present unless they were administered or added intentionally.

Concentration of Alcohol in the Blood.—With oral administration of a single dose, this ascends as a parabolic curve, with the maximum in one-half to two hours, in most cases between thirty and sixty minutes (Carlson *et al.*, 1934, give a succinct bibliography). It remains at this highest level for some time (the "Grehant plateau") and then descends gradually. The ascent is determined chiefly by the rate of absorption.

If adequate time elapses, the concentrations are practically identical in samples of blood from the arteries, veins and capillaries, and from different areas (Liljestrand and Linde, 1930), including the fetal blood (Kostitch, 1922), and also in the cerebrospinal fluid and the fluids of the eye; but it may take more than one hour to secure equilibrium, largely because of differences in the local circulation. For instance, when rats were killed by intraperitoneal injection of alcohol, 20 mg. per Gm., the concentrations (per cubic centimeter) found in the blood at the moment of death were: right heart, 16.0 mg.; arterial blood, 15.8, jugular vein, 9.4; femoral vein, 6.3 (Haggard and Greenberg, 1937).

Influence of Conditions.—The blood concentration course is not constant even for the same individual under like conditions; but *changed conditions* do influence it in definite directions (Tuovinen, 1930):

Fasting or with Food.—The blood concentration rises somewhat higher if the alcohol is consumed fasting (as the preprandial cocktail) than with food (Widmark, 1915; Southgate and Carter, 1926; Tuovinen, 1930), owing to the more rapid passage into the duodenum. The difference, however. is not great.

Concentration in Which the Alcohol is Taken.—The results are so contradictory that the effect may be considered negligible: It has been reported that the concentration in the blood rises with the concentration in which the alcohol is taken (Simonin, 1930); that it is higher between 5 and 20 per cent than between 40 and 60 per cent (Tuovinen, 1930); and that it makes no material difference (Widmark, 1915).

Muscular exercise tends to lower the concentration somewhat (Cassinis and Bracaloni, 1930), by the increased pulmonary ventilation; but the difference is scarcely appreciable (Carpenter and Lee, 1938). Increased *altitude* above sea level (Biehler) and presumably also *fever* would similarly tend to lower the concentration; but the concentration is reported to rise more rapidly at high altitude, and (temporarily) to a higher level (R. A. McFarland and Forbes, 1936). The administration of *dextrose* (25 Gm.) with insulin (15 units) to acutely intoxicated individuals doubled the rate of fall of alcohol concentration in their blood (W. Goldfarb *et al.*, 1939). *Insulin* alone has no effect on the alcohol concentration or symptoms even in diabetic patients. Injection of *posterior pituitary* extract lowers the alcohol concentration, in normal individuals and in diabetes insipidus. *Diuresis by increased water intake* does not alter the concentration materially (Blotner, 1939).

Habituation.—The blood concentration generally rises and falls more rapidly in those accustomed to alcohol; the peak concentration may be higher or lower than in abstainers, but it is not maintained as long (Fleming and Stotz, 1935; Bogen, 1927). The chief cause of the tolerance, however, is psychic adaptation to the effects.

The *actual concentration with different doses* averages close to a peak blood concentration of 0.001 per cent of alcohol per 1 cc. of alcohol ingested (about two-thirds of the concentration which would obtain had all been absorbed and none destroyed). Conversely, the peak concentration of 0.01 per cent would be attained by 10 cc. of alcohol, 25 cc. (nearly an ounce) of whisky, or 300 cc. (nearly a bottle) of 3.2 per cent beer.

The *urine concentration* ranges from one-half to twice the concentration of the blood, but one and one-third may be taken as a fair average; or conversely, the blood concentration may be taken as three-fourths of the urine concentration (Carlson *et al.*, 1934; Bornstein and Budelmann, 1930). The error probably falls well within the range of variation of physiological response, so that the urine determination may be substituted when blood is not practicable, especially if the bladder is emptied in half-hour intervals. Absorption of alcohol from the bladder is insignificant with concentrations that occur after alcohol is drunk (H. W. Haggard *et al.*, 1940). Diuresis by forced water intake does not alter the alcohol concentration of the urine (Blotner, 1939). Glucose administration also has little effect (Carpenter and Lee, 1937).

Cerebrospinal Fluid Concentration.—Alcohol is excreted freely into this fluid (as are also acetone and chloroform, Hald, 1911), and this has long been used for the diagnosis of alcoholic psychosis (Selig, 1913), as demonstrable quantities may persist for ten days (Lenoble and Daniel, 1917). Its concentration curve is similar to that of the urine and blood (Bogen, 1927); but there is a distinct lag in the ascent, especially with the lumbar fluid, even after intravenous injection. With oral administration, when the peak concentration is reached in twenty minutes for the blood, the cisternal fluid does not reach this level till after fifty minutes, and the lumbar fluid not till after three hours; so the intoxication symptoms are at their height when the lumbar fluid concentration is still low. This is therefore useless for the chemical diagnosis of alcoholic intoxication unless an hour or, better, three and a half hours have elapsed (Newman and Mehrtens, 1933). It is not clear why it should be used even then, since the urine and expired air are at least equally reliable, and the blood is more so.

Gettler, 1931, reported that the *brain* shows somewhat lower alcohol concentrations than the cerebrospinal fluid, probably because of its lower water content. *Epinephrine* potentiates the depressant action of alcohol. U. Friedemann ascribed this to increased permeability of the brain capillaries, "auxoneurotropic" action. Hulpieu and Cole, 1946, attribute it to alteration in the circulation.

The *saliva concentration* agrees closely with the blood and may be used as index of intoxication (Abels, 1936).

Ocular Fluids and Lens.—Nicloux and Redslob, 1931, found the concentration in the vitreous humor the same as in the blood; that of the lens was about one-half.

The *expired air* gives a fairly uniform relation to the alcohol concentration of the blood (Liljestrand and Linde, 1930), especially when the dilution with tidal air is discounted by determining the ratio of alcohol to CO_2: the weight of alcohol per 190 mg. of CO_2 (about 4 liters of expired air) equals the weight of alcohol per cubic centimeter of blood (Harger, Lamb and Hulpieu, 1938; details of method). The concentration in the air is highest inthe first fifteen minutes after ingestion, and is low in three hours (Carpenter and Lee, 1938).

Relation of the Alcohol Concentration (in the Blood or Urine) to Inebriation.—These correlate closely in a given individual so that they may be used as a *chemical* test of drunkenness; but different individuals do not react equally. The following compilation gives the usual range of responses, to increasing venous blood concentrations, which is the most reliable criterion (Ellerbrook and Van Gaasbeek, 1943); for the urine these would average a third higher. In translating these back to dosage, it may be accepted that the alcohol concentration of the blood is practically in simple proportion to the quantity taken, and that between half an hour and five hours after taking it, 0.01 per cent of alcohol in the blood corresponds to a dosage of 10 cc. of alcohol, or 1 ounce of whisky, or a 12-ounce (300 cc.) bottle of beer. The compilation indicates little if any change below 0.01 per cent; somewhat decreased competence with 0.015 per cent, and definitely decreased competence with 0.06 per cent; with 0.1 per cent a third of the subjects are diagnosed clinically as inebriated; at 0.15 per cent half are so diagnosed. This is generally accepted as the "critical concentration" for the *chemical diagnosis of drunkenness, i. e.,* 0.15 per cent in the blood, or 0.2 per cent in the urine or 1 mg. per liter of expired air; corresponding to 150 cc. of alcohol, or about a pint of whisky or about ten bottles of beer. This may be justifiable as a basis for legal action, but it should be remembered that a third of the subjects reach this stage with two-thirds of the concentration and that a tenth of this quantity impairs judgment.

Various "raw" liquors, "moonshine," and the like, all give the same concentrations for the same degree of intoxication (Bogen, 1927).

The compilation is chiefly from Bogen (B); from Carlson and associates (C), 1934, on beer; from Tuovinen (T), 1930; from Miles (M), 1933; and from Widmark (W), 1932 and 1934. Widmark's series covers the official reports on automobile accidents in Sweden, some 560 cases by 1932, including the clinical diagnosis by the physicians (150 in this series), and the chemical determination in the blood by Widmark's micro-method (Biochem. Ztschr., *131:* 473, 1922), which includes acetone, acetaldehyde, glycerol and organic acids; but their variation is negligible in comparison with alcohol.

Correlation of Alcohol Content of the Blood (Per Cent) with Clinical Symptoms.—*Effects doubtful:* 0.006 to 0.01: Initial stimulation phase begins (T); behavior tests practically normal (B and others).

Effects slight (0.01 to 0.05 per cent):

0.015: Decreased accuracy in typing tests and increased seriousness of automobile accidents (Heise, 1934),

0.02: Subjective effects: Slight dizziness, warmth, comfort; pleasant, sociable (M); although

0.027: Showed no change in other types of performance tests, or in visible behavior (C).

0.03: Mild euphoria, feeling of "good fellowship" (M); visible behavior and behavior tests, practically normal for most.

0.05: "On top of the world"; normal inhibitions greatly weakened, boastful, clumsy.

Effects definite, but not marked (0.06 to 0.1 per cent):

0.06: Notable decrease of motor control (Romberg test) in C's series. One subject in fourteen showed incoordination and loss of control.

0.07: Feeling of remoteness; upsets chair on rising (M). In the W series, none under 0.08 were diagnosed clinically as inebriated, but between

0.08 to 0.1: A third were diagnosed as conspicuously "under the influence"; at

0.1: Staggers perceptibly; talks to himself; speech slurred and confused; fumbles long with keys (M).

0.15: Definitely drunk, but not helpless. Half were diagnosed as under the influence in the W series. In C's series with beer, the performance tests were distinctly poorer, eleven subjects in twelve showed gross changes in behavior, and two out of three vomited.

Helpless and fatal (0.2 per cent upward):

0.2: Emotional and cross; needs help to walk or undress; one in five unable to speak; nauseated; poor control of urination (M).

0.225: Practically all were diagnosed as inebriated (W).

0.265: All were so diagnosed (W).

0.3: Stuporous, sleeping and vomiting by turns; combative when aroused.

0.4: Comatose in most cases.

0.5: Always fatal clinically, generally several hours or even days after onset of coma. Death sometimes occurs with considerably less than 0.5 per cent (W. W. Jetter, 1943).

For dogs, Turner 1932, found definite intoxication with 0.25 per cent; pronounced with 0.3, stupor with 0.4 per cent. Death did not occur with 0.55 per cent.

A "*critical concentration*" of *drunkenness,* widely accepted for legal purposes, is 0.15 per cent in the blood, 0.2 in the urine, generally equivalent to 150 cc. of alcohol, about a pint of whisky, or about ten bottles of beer; but it should be remembered that one in three may reach this state with two-thirds of the quantity; and that a tenth of this quantity impairs judgment. On the other hand, at 0.15 per cent, half were diagnosed as not drunk, and even at 0.18, one in five escaped this diagnosis, in the (W) series. Other studies (S. Smith and Stewart, 1932) have confirmed the variability of the borderline concentrations in different individuals as to psychological and police tests. The A.M.A. Committee of 1939 recommended that persons with less than 0.05 per cent by weight of alcohol in the blood (or corresponding amounts in other fluids) should not be prosecuted for driving "while under the influence of alcohol"; those with 0.05 to 0.15 per cent only if physical examination gives definite confirmation of being "under the influence"; and that 0.15 per cent or more should be considered sufficient evidence of such detrimental "influence." The National Safety Council, 1944, made analogous recommendations.

Epinephrine, if administered before the alcohol, increases the narcosis beyond what would correspond to the blood level (the *auxoneurotropic* action of Friedemann). This is attributed to the diversion of a greater quantity of alcohol to the brain, by the epinephrine contraction of the blood vessels in other areas (H. R. Hulpieu and Cole, 1946).

Blood Sugar Level and Fatal Dose.—Haggard and Greenberg, 1937, reported for fasting rats that the alcohol concentration in the jugular vein blood at the moment of death varies directly with the blood sugar level, so that death occurs at 0.8 per cent of alcohol with 0.07 per cent sugar; at 0.95 per cent with 0.1 per cent of sugar; and at 1.2 per cent alcohol with 0.2 per cent of sugar. The blood sugar therefore appears to protect against alcohol fatality. The explanation is not clear.

Habituation on the Response to Concentration.—Bogen, 1927, reported that at any given concentration level, habitual drunkards show the same symptoms as those not accustomed to alcohol, but this lacks confirmation. In rats, habituated animals require a higher concentration of alcohol in the brain for intoxication than do normal animals (Jeanne Lévy, 1934).

Castration lowers the resistance of female rabbits to the acute narcotic action of alcohol, and their resistance is increased by administering estrone, so that intoxication requires higher blood levels. The general metabolism of alcohol is not affected; thus the mechanism appears to be central (L. Goldberg and Störtebecker, 1943).

Existence of Alcohol in Normal Tissues.—A trifling quantity of alcohol appears to be produced in the tissues in the course of normal metabolism. Its presence was claimed by W. H. Ford, 1872, confirmed by Landsberg, 1904, and identified through transformation into ethyl iodide by Gettler, Niederl *et al.*, 1932; but the quantity is extremely small. In human material, Hargen and Goss, 1935, found none to 0.027 mg. per 100 Gm. in the blood; 0.05 to 0.12 in the brain; 0.085 to 0.227 in the liver; 0.044 to 0.142 in the kidneys; and 0.060 to 0.185 in the urine. Hog brain contained 0.47; dog's, 3.0. McNally, Embree and Rust, 1937, found 1.1 to 5.2 in human placenta. The highest figure for urine is only a twentieth of the lowest concentration that gives recognizable effects. Reach, 1907, reported that fresh rabbit's muscle contains to 0.0017 per cent of alcohol; the liver may contain 0.02 to 0.14 per cent. Voeltz and Dietrich, 1915, recovered a total of about 0.1 cc. from normal dogs. Dakin believed that this "normal" alcohol is not formed in the tissues, but by intestinal fermentation; but Taylor, 1913, found it even after the removal of the entire digestive tract.

Acute Alcohol Poisoning.—The *narcotic stage* is characterized by a combination of most or all of the following symptoms (British Association Committee): odor of breath or vomitus; dry furred tongue, or excessive salivation; irregularity of behavior—insolence, abusive language, loquacity, excitement, sullenness, disorder of dress; suffusion of conjunctiva; abnormality of pupils, which may take various forms; convergent strabismus (esophoria), but with undiminished visual acuity (Colson, 1940); hiccup; loss or confusion of memory, especially of recent events, and of appreciation of time; speech hesitant, thicker; impaired articulation; tremors; errors of coordination and orientation: Romberg sign, manner of walking, of turning sharply, of sitting down and rising, of picking up coin or pencil from the floor.

The *anesthetic stage* sets in as consciousness, sensation and muscular tonus are gradually lost. The plasma volume is increased by withdrawal of tissue fluid to dilute the Na and Cl retained by temporary renal impairment (W. B. Nicholson and Taylor, 1940).

In the *paralytic stage* proper, the symptoms are those of beginning medullary paralysis: the respiration is slow and stertorous; the pulse, scarcely discernible; the skin, cold and cyanotic; the pupils are generally dilated; the reflexes, abolished. The temperature falls severely. The odor of the breath is diagnostic. If large doses have been taken on an empty stomach, the paralytic symptoms may set in at once.

Recovery.—The coma—if the intoxication has progressed so far—passes into natural sleep, often with sweating. On awakening there follows a series of symptoms, the "hangover," pointing mainly to *acute gastric catarrh*, and perhaps to cerebral edema and to functional neuritis, and grouped by the Germans under the name of "Katzenjammer": headache, coated tongue, loss of appetite, irritable stomach, diarrhea, muscular pains, and so forth, The *skin*, after severe alcoholic poisoning, may show effects resembling those of contusions or burns: edema, blisters, extravasation of blood, and gangrene. Bedsores are common. A few cases of total functional blindness of both eyes have been reported, with normal pupillary reactions and normal fundi. They improve rapidly (F. D. Carroll and Goodhart, 1938).

Death is relatively rare. It may occur within half an hour, or the coma may grow deeper and terminate in paralysis of the respiration or the heart, or in pulmonary edema, generally within twenty-four hours. If the coma lasts beyond thirteen hours, recovery is exceptional. Death may also occur later, either from prolonged coma, or after a protracted debauch, as the result of gastric irritation and exhaustion. The *acute fatal dose* is probably variable. In analogy with animals, it would require about a quart of whisky; cases of death from a pint are recorded (Lewin). With children, 100 to 200 cc. of 50 per cent alcohol is fatal.

Treatment of Acute Alcohol Poisoning.—*Ordinary drunkenness* treats itself adequately with time and sleep. Strong coffee or aromatic spirits of ammonia may serve as temporary stimulants, and paraldehyde as sedative. With *severe intoxication*, the stomach should be evacuated by lavage or perhaps preferably by apomorphine, which acts also as hypnotic. With *coma*, dextrose may be injected intravenously. Dangerous depression of respiration and cyanosis indicate oxygen inhalation, especially as alcohol intoxication increases the susceptibility to oxygen deficiency (Barach, 1934); but practically the benefit is not great (Butler, 1936).

The addition of 5 or 10 per cent of carbon dioxide has been advocated to promote pulmonary ventilation, but this effect is insignificant and does not modify either the symptoms or the toxicity (Newman and Card, 1936; Fleming and Reynolds, 1935). However, H. W. Haggard *et al.*, 1940, reported that CO_2 inhalation by stimulation of the respiratory center definitely increases the blood concentration which must be attained to stop respiration (normally, 0.89 to 1 per cent). The following did not alter the fatal level: caffeine, dinitrophenol, strychnine, amphetamine, sodium bromide, acetanilid and related antipyretics. Morphine lowered the fatal level markedly. Pilcher, 1912, had shown that the administration of caffeine is useless in serious poisoning and may be detrimental. Amphetamine, metrazol, picrotoxin and coramine have a limited mutual antagonism with alcohol in rabbits (H. W. Werner, 1939), but it is doubtful whether they should be used clinically. Amphetamine, for instance, lightens the narcosis of moderate doses of alcohol, but increases the toxicity of near-fatal doses (Reifenstein, 1940). The *"morning after"* may be treated with coffee, analgetics, bromide, magnesia, bicarbonate or citrate (against the acidosis; B. B. Clark and Morrissey, 1938), and, if severe, by gastric lavage.

Poisoning by Denatured ("Industrial") Alcohols.—Alcohol for industrial use is mixed with nauseant, irritant and toxic substances to render it unfit for drinking and so secure exemption from the internal revenue tax. The Journal of the American Medical Association, 1920 (*74*:343), describes the usual formulas. The "*Industrial Methylated Spirit*" of the B.P. is a mixture of 19 volumes of alc. (95 per cent) with 1 volume of wood naphtha, chiefly methyl alcohol. Such spirits produce the effects of the added poison along with those of the alcohol, and are much more dangerous than ethyl alcohol. The use of wood alcohol for denaturing industrial alcohol is especially unfortunate, since prolonged exposure to vapors from alcohol containing only 4 per cent of methyl alcohol has given toxic eye symptoms (J. M. Robinson, 1918). The drinking of spirits containing only 1 per cent of wood alcohol is said to result in visual disorders, generally after three or four months, or with large doses (Eleonskaia, 1916).

Peculiarities of Alcoholic Beverages and their "Impurities."—Whisky, brandy and other distilled spirits that contain 40 to 50 per cent alcohol are termed *"potable" spirits*, since higher concentrations cannot be conveniently swallowed until they are diluted, because of the choking reflexes from the local irritation. The fresh or "raw" distillates, including "moonshine" and other illegitimate liquors, contain other higher alcohols and ethers and esters formed from these, called collectively "fusel oil," sufficient to give a strong and disagreeable flavor. These may be removed almost completely by fractional distillation (completely so for synthetic alcohol), yielding the nearly unflavored "neutral spirits"; or they may be diminished and modified by "aging" in wooden barrels, especially charred, for two years or longer. This gets rid of the disagreeable substances, by adsorption and oxidation, and develops the desired bouquet, through formation of the so-called "oenanthic" ethers. This process, which furnishes the "straight" liquors, entails considerable loss by evaporation, as well as the storage costs (storage in glass does not age distilled liquors). Various shortcuts have been devised, especially dilution of unaged or partly aged liquors with neutral spirits, resulting in "blended liquors"; but this term may also be applied to mixtures of naturally aged spirits. "Factitious liquors" are made by adding flavoring substances to neutral spirits.

The impression prevails that the "impurities" add materially to the harmfulness of the liquors, but practically all scientific investigations have confirmed the conclusion that there is practically no objectively discoverable difference in action between any of the potable spirits, ranging from the rawest to the most delicate. They are all about equally and insignificantly more irritant and more toxic than pure ethyl alcohol. The differences are purely in the flavor and its psychic suggestions. This could be deduced from the nature and quantity of the impurities. The "*fusel oil*" of raw grain alcohol, which is popularly considered the chief offender, amounts to only 0.2 per cent of the alcohol, corresponding to 0.08 cc. per 100 cc. of whisky; and about 95 per cent of this small quantity consists of amyl, butyl and propyl alcohols (Bell, ref. report of Select Committee, British Parliament, 1891), which are but little more toxic than ethyl alcohol; the unidentified remainder, amounting to only 4 mg. in the 100 cc. of whisky, is no more toxic. Acetaldehyde in raw whiskies may amount to 0.1 per cent (Doran and Beyer, 1923), and this might add slightly to the local irritation, but evidently not enough to be appreciable. *Furfurol*, (about 0.005 per cent in "pot still" liquors) formerly believed to modify the intoxication, does not appear to do so. (Larger doses are convulsant, Laborde, 1888; McGuigan, 1923. It is used as a paint and varnish remover; Gardner, 1923.)

Various Royal British Commissions which have investigated the subject scientifically have all come to the conclusion that the fusel oil is distasteful but not harmful even in the worst specimens examined by them; but the cheaper liquors are likely to be consumed in larger quantities and in debauches, which probably accounts for their sinister reputation. In animals and patients, Chopra, 1927, found the toxicity essentially identical for aged, immature and "factitious" spirits. Bogen, 1927, found that various "raw" liquors give the same degree of intoxication for the same blood concentration of alcohol, as does alcohol itself or aged spirits. Barlow, 1936, in an extensive experimental investigation on animals and men, comparing the purest synthetic ethyl alcohol, pure grain alcohol, blended whisky and straight whisky, found no difference in any respect qualitatively and practically none quantitatively, although the toxicity and local irritation did increase slightly in the order given. Perhaps the only investigation that suggests a difference is that of MacNider, 1924, who reported a greater tendency to albuminuria in dogs, for "moonshine" liquors; but this is not a common feature in clinical intoxication.

As to other liquors, most of the traditional differences probably depend upon the circumstances under which they are ordinarily consumed. *Brandy* does not differ from whisky except in flavor. With *gin*, the juniper iol, adds to the diuretic action. *Beer* is diuretic by the volume of its water, and its somnifacient action is probably enhanced by the lupulin of the hops. *Absinthe* gradually niduces mental hallucinations.

The annual per capita consumption of alcoholic beverages in the United States in 1936 was estimated as 11 gallons of beer, 1 gallon of distilled liquors, and 0.44 gallon of wine (J. A. Waddell and Haag, 1938).

***Alcohol**, U.S.P. (Ethanol, Spiritus Vini Rectificatus), contains not less than 92.3 per cent by weight, 94.9 per cent by volume, of C_2H_5OH. Colorless, volatile liquid, of characteristic odor and burning taste. Freely miscible with water, ether, chloroform, and so forth. Since condensation occurs on mixing alcohol and water, the percentage of the resulting product cannot be deduced by a simple ratio. Tables for making the commonly needed percentages by the dilution from the official alcohols are given in the U.S.P. and B.P. *Dehydrated Alcohol*, U.S.P. (Absolute Alcohol or Ethanol), is not less than 99 per cent by weight of C_2H_5OH. Very hygroscopic. *Diluted Alcohol*, U.S.P., a mixture of equal volumes of official alcohol and water, contains 41 to 42 per cent by weight or from 48.4 to 49.5 per cent by volume of C_2H_5OH.

Whisky, N.F. (*Spiritus Frumenti*), is an alcoholic liquid obtained by the distillation of the fermented mash of malted cereal grains, and contains between 47 and 53 volume per cent of alcohol. It must be aged in wood at least two years. *Brandy*, N.F. (*Spiritus Vini Vitis; Spir. Vini Gallici, Cognac*), is distilled from grape wine and contains 48 to 54 volume per cent of alcohol, aged in wood for at least two years. Other distilled spirits have about the same alcohol concentration: *Holland Gin*, distilled over juniper berries; *Rum*, from molasses; *Arrack*, from rice, and so on.

Wines are made by fermenting the expressed juice (must) of the grape. If this contains the skins of dark grapes, the wine will be red; if made from light grapes, or from the juice of dark grapes without skins, it is "white," *i. e.*, an amber color. A wine which contains much alcohol (15 to 20 per cent) is "generous"; one poor in alcohol, "light"; one containing much sugar, "sweet"; poor in sugar, "dry." If it contains CO_2 it is "sparkling"; if tannin, "rough" or "astringent"; if acid tartrates, "acidulous."

Malt liquors contain alcohol, CO_2, sugar and usually hops. The color varies from pale amber to dark brown, the difference being due mainly to charring of the malt. Lager beer is made by slow fermentation at a low temperature; porter, ale and stout, by rapid fermentation at a higher heat.

The alcohol percentage of the principal alcoholic beverages is (by volume): 18 to 23 per cent: Sherry (Vinum Xericum), Port (Vinum Portense), Madeira, Marsala, Tokay, Malaga. 10 to 17 per cent: Champagne, Claret, Rhine Hock), Catawba. 6 to 13 per cent: Cider (from apples) (Perry (from pears) and other fermented fruit juices

3.5 to 7 per cent: Ale, Porter, Stout and Export Beers.
2.5 to 3.5 per cent: Lager Beers, Fermented Milks (Kumiss, Yogurt).

THE HABITUAL MODERATE USE OF ALCOHOL

A certain amount of alcohol, varying for individuals, may be taken occasionally or daily without demonstrable permanently injurious effects. The relaxation, the easing of strain, of maladjustments, of excessive self-consciousness, of excessive inhibitions, indeed the euphoria, may sometimes be beneficial; but they may also lead to diminished efficiency, especially in accuracy; impaired judgment; increased liability to automobile accidents; loss of self-reliance; perhaps diminished resistance to disease; danger of excesses, periodic or continuous; higher incidence of venereal diseases; and general disrespect for law and order. On the other hand, the moderate use of alcohol is often blamed for shortened duration of life and for various physical injuries, without adequate data, or on the basis of effects produced only by large quantities.

The Research Council on Problems of Alcohol, 1946, claims that fifty million persons in the United States take alcohol, that 6 per cent of these become excessive drinkers, and that 1½ per cent become chronic alcohol addicts. The amount spent annually in the United States on alcoholic drink is given as seven billion dollars.

Duration of Life.—It has been claimed, on the basis of life insurance statistics, that the average duration of life is distinctly less for those who habitually drink alcohol, even in moderate quantity, than for total abstainers. Raymond Pearl, 1938, considers that this deduction is mistaken, and that there happens to be rather an increase. Heavy drinking definitely shortens longevity. Rats receiving 5 per cent of ethyl alcohol in their drinking water, and averaging for nine months a daily consumption equivalent to 2.1 cc. of absolute alcohol per Kg. of body weight, are somewhat sluggish and stupid, but their mortality rate was not significantly different (L. L. Boughton, 1944). On the other hand, Arlitt, 1919, claimed that the duration of life is shortened.

Diminished Resistance to Pneumonia and Other Infections.—Capps and Coleman, 1923, found that the mortality rate in 3500 pneumonia patients at Cook County Hospital rose from 22.5 per cent for total abstainers and occasional drinkers, to 34.4 per cent for "moderate" drinkers, and 49.9 per cent for heavy drinkers. The "moderate," however, extended over a heterogeneous group, from the daily consumption of a glass of beer to heavy drinkers and occasional drunkenness. Increased susceptibility to *other infections* has been demonstrated experimentally on animals acutely intoxicated by alcohol. This may be explained by the observation of Pickrell, 1938, that alcoholic stupor breaks down the resistance of rabbits previously immunized to pneumococci, by changes in the capillary endothelium which prevent the dilatation and increased permeability with which it normally reacts to infection, in this way hindering the emigration of protective leukocytes. Polynuclear leukocytes also fail to gather about bacterial injections into the skin of alcoholized rabbits (R. H. Rigdon, 1943). Mueller, 1904, Wirgin, 1905, and others found that the *formation of antibodies is lessened* if rabbits are kept mildly intoxicated for several days after the injection of an antigen. Laitinen, 1907, reported that small doses (0.1 cc. per Kg., daily) suffice to render the erythrocytes less resistant to hemolysis, and also lessen the resistance to infectious diseases. He asserted that this lessened vitality is transmitted to the offspring. For human subjects, Reich, 1915, claimed diminished resistance of erythrocytes to hypotonic solutions, and slight decrease of the bactericidal action of serum against typhoid bacilli. The effects, however, varied greatly, so that it is difficult to estimate their importance. Phagocytosis was not affected.

Diminished Resistance to Poisons.—Hunt, 1907, found that the long-continued administration of small quantities of alcohol to mice or guinea pigs increases their susceptibility to the fatal action of *acetonitrile.* This is attributed to a derangement of metabolism which hastens the decomposition of the nontoxic nitrile into the cyanide. It is not produced by methyl alcohol, chloral, and so forth.

CHRONIC ALCOHOLISM

The excessive use of alcohol, the habitual consumption of large quantities for long periods, leads to functional and organic changes, the latter compounded of local irritation, capillary injury, fibroses, neuritis, and others less definite. The most frequent lesions are mild inflammation and possibly atrophy of the gastric mucosa; edema and congestion of the brain and meninges; possibly minor alterations in the kidneys; occasionally hepatic cirrhosis (A. W. Wright, 1941). The effects are partly direct, partly the result of malnutrition and vitamin deficiency, which are difficult to disentangle.

Gastro-Intestinal Irritation.—The first results are local, and depend largely on the concentration of the spirits; but vitamin deficiencies and nervous irritability play a part. Catarrh of the alimentary canal progresses from the pharynx downward, with the usual symptoms of catarrhal gastro-enteritis: loss of appetite, gastric distress, irregularity of stools, craving for spices, and so on. In excessive beer drinking the habitual overdistention of the stomach leads to chronic dilatation.

Seventy per cent of the patients with chronic alcoholism are said to have gastric disorders; 50 per cent, achylia; 40 per cent, morning nausea. However, W. B. Seymour Spies and Payne, 1939, found their group of chronic alcohol addicted patients singularly free from gastric complaints. L. H. Berry, 1941, observing a hundred persons with chronic alcoholism of long standing, found definite gastritis in about a third, mild gastritis in another third, and no gastritis in the remaining third. An extensive *review* of the effects of alcohol on the digestive tract is given by Beazell and Ivy, 1940.

Malnutrition and emaciation result from the gastro-intestinal irritation, nervous disturbances, vitamin deficiencies and generally inadequate food, owing to anorexia and often to economic distress. The malnutrition in turn is partly responsible for the neuritis, the central nervous disturbances and the skin changes.

Growth.—Daily consumption of alcohol by young rats, in doses of 2.5 to 10 cc. per Kg. for twenty weeks, produced prompt and marked retardation of growth. The effect was about as marked with the lower dosage as with the higher, and with dilutions of 2½ per cent as with 10 per cent (Sollmann, 1920).

Degenerative Changes in Internal Organs.—The continued presence of alcohol in the body sets up a series of low grade irritant and degenerative phenomena in various other organs with which it comes in contact. These changes consist in fatty infiltrations, cellular degeneration, and hypertrophy of connective tissue. They involve chiefly the liver (cirrhosis) and the kidneys. The dilatation of the skin vessels (bibulous nose, acne rosacea) may be diagnostic. Statistical studies indicate, however, that alcohol is not concerned in arteriosclerosis (Cabot, 1904, autopsies) or angina pectoris. The incidence ratio of heavy, light and nondrinkers is practically the same for patients with angina as for those with normal hearts (White and Sharber, 1934).

The necrotic changes in the tissue cells may be attributed to the continued irritation from the constant presence of the alcohol; to this must be added the interference with circulation due to the changes alcohol causes in the blood vessels. Both concur in the production of the degenerations. Of these, the fatty are the most common, since alcohol, by its combustion, prevents the normal consumption of fat. Repeated administration of alcohol to dogs, for several days, uniformly increased the *total fat of the liver*, sometimes to 300 per cent. The *cholesterol content* was also somewhat increased (Ducceschi, 1918). Connective-tissue formation results as a consequence of necrosis of the parenchyma.

Hepatic cirrhosis has a definite connection with chronic alcoholism, which probably acts as a predisposing cause, by interference with proper nutrition, producing successively fatty infiltration, perilobular fibrosis and eventually portal cirrhosis (C. L. Connor, 1938; C. H. Greene, 1943). *Pancreatitis* has also been reported (E. Clark).

In America, half to two-thirds of the patients with Laënnec's cirrhosis have a history of excessive alcohol consumption (Ratnoff and Patek, 1942); the frequency of cirrhosis was notably less during the prohibition years (N. Evans and Gray, 1938). Cirrhosis, however, develops in only a minority of alcoholic subjects, variously estimated as 1 to 30 per cent (Ratnoff and Patek); and about two-thirds of the deaths from cirrhosis are of noninebriates (Jolliffe and Jellinek, 1942). There is no satisfactory evidence that alcohol produces cirrhosis directly; nearly all investigators agree that it does not do so in animals, nor do contaminants of alcoholic beverages give clear-cut results (review, P. György, 1944).

Dietary hepatic cirrhosis is produced in rats by diets deficient in protein, specifically of methionine, and vitamin-B-complex factor (György and Goldblatt, 1942). The chief factor is a high ratio of cystine : methionine, and improvement follows if methionine is increased (P. György, 1944). Addition of alcohol to the deficient diet increases the cirrhosis (J. V. Lowry *et al.*, 1942).

Defective diet is a common occurrence in chronic alcoholism, and furnishes the presumptive explanation. Patek and Post, 1941, claimed amelioration of clinical cirrhosis by diet rich in the B complex.

The degenerative changes in the *kidneys* lead to nephritis, with cirrhosis, albuminuria, diminished secretion of urine, secondary weakening of the heart, and so forth; but there is no conclusive evidence that alcohol is a causative factor in Bright's disease or arteriosclerosis (review, M. Bruger, 1940). The *heart* itself, however, in common with skeletal muscle, shows primary fatty degeneration. This, together with the atheroma, and so on, leads to hypertrophy and dilatation of the viscus, and later to dropsies, and like results. The heart rate is generally rapid. The fatty changes in *voluntary muscle* lead to muscular debility, especially in beer drinkers, in whom there is more material for fat formation. *Gout* is a common sequence of moderate alcoholism. The *respiratory organs* show chronic catarrhal inflammation of the passages, and a disposition to fatal pneumonia. *Changes in the skin*—vascular ecchymoses, acne rosacea, disposition to furuncles and carbuncles—may be counted among the earlier actions.

These various anatomic lesions of important organs result in a pronounced *lowering of resistance*, and a high mortality with infectious diseases and operations. It appears that the amount of antitoxic complement is lessened.

Experimental chronic alcoholism, in rabbits, produced fatty changes in the heart, liver and kidneys, and cellular infiltration of the pia (Lissauer, 1913). Hepatic changes occur also on intravenous injection (Schafir, 1913). In the heart, Otto, 1914, found degenerations of ganglion cells, atrophy of muscle, and scar tissue. Large single doses (4 cc. per Kg.) may also cause changes. Single small doses do not leave any lesions (v. Otto, 1914).

Nephrotoxic Effects in Dogs.—MacNider, 1925, reported that whisky produces much more damage than pure alcohol. He described albuminuria, polyuria, fatty infiltration of the glomerular vessels, more severe in dogs which were already nephropathic.

Nervous phenomena may be central and peripheral, organic and functional. Tremor of the hands and tongue sets in early; *periph-*

eral neuritis comes later, chiefly from vitamin deficiency. Optic neuritis occasionally results in blindness.

Vitamin deficiency as the causative factor in alcoholic polyneuritis was suggested by G. C. Shattuck, 1928, and G. R. Minot, 1929. It was established by Blankenhorn and Spies, 1935, who found that polyneuritis is curable by vitamin rich diet, even though the patients continued to consume whisky at the rate of a pint to a quart daily. Jolliffe, Colbert and Joffe, 1936, confirmed that the incidence (or absence) of polyneuritis in alcoholic addicts corresponds closely to *thiamine deficiency* in their diet and that marked improvement occurred with the administration of this substance (Jolliffe and Colbert, 1936). However, M. R. Brown, 1940, found that a series of patients with alcoholic polyneuritis improved quite as well on the ordinary hospital diet as when intensive thiamine and parenteral liver therapy were added. Ethyl alcohol mobilizes *vitamin A* from its tissue stores, increasing its concentration in the blood (S. W. Clausen *et al.*, 1940), and causing temporary improvement in twilight vision (Pett, 1940).

Mental Manifestations.—Lassitude and diminished activity and changes of temperament (confirmed on mice; Nice, 1912) occur early, followed considerably later by mental deterioration, habituation, stultification, and sometimes hallucinations, delirium tremens, paranoia, Korsakow's psychosis; also organic brain changes and neuritis (review, Seliger and Cranford, 1945). A good part of the mental phenomena are only indirectly related to alcohol, and in many instances they are the cause rather than the result of alcoholism.

Ten to 30 per cent of the cases of *insanity* have been attributed directly to alcoholism; but Heron, 1912, found the proportion of mental defects as high in the recent as in old cases of alcoholism. *Epilepsy*, which is a hereditary nervous disease, is seventy times as frequent in alcoholics as in the general population. These facts illustrate how frequently alcoholism is the result rather than the cause of mental degeneration.

Alcoholic mental disease may result from either regular or periodic drinking. It generally comes only after many years of heavy drinking, averaging twenty-two years for men, fifteen years for women. About a fourth of these patients give a history of delirium tremens (H. M. Pollock, 1940). *Anatomic changes* are reported as chronic meningitis with thickening; serous effusions into ventricles; softening; tendency to hemorrhages and apoplexy. Histologically, shrinkage and alterations in the staining properties of the cells and changes in the dendritic processes have been averred. They may be ascribed principally to the vitamin deficiencies (L. Alexander, 1941; Scheinker and Aring, 1943).

Delirium Tremens.—This peculiar manifestation, chiefly an acute and temporary mania, with hallucinations and delusions of persecution, may occur in drunkards continuously consuming large quantities of alcohol, but generally at the end of a prolonged alcoholic debauch, especially when joined with inanition and exhaustion, exposure, overexertion, trauma, hemorrhage, operations, psychic shock or any serious illness, especially pneumonia. It is not likely to occur in "Saturday-night drinkers," or in a periodic drinker unless a high concentration of alcohol is maintained for many days (Doane, 1939). It was formerly thought that sudden withdrawal of the alcohol could bring on an "abstinence delirium," but this is doubtful (Holitscher, 1908). Inanition plays a definite part in provoking the attack, through vitamin deficiency which is especially detrimental to the carbohydrate metabolism of the central nervous system. Administration of thiamine shortens the attack even though the alcohol consumption is continued (H. E. Kiene *et al.*, 1940), and nicotinic acid (0.6 Gm.) is reported to be even more effective (Mainzer and Krause, 1939).

The *symptoms* begin with a day or two of premonitory restlessness, tremor, insomnia and anorexia. They pass into excessive tremor, persistent insomnia, violent and talkative delirium and terrifying hallucinations of sight, touch and sometimes hearing. The attack runs its course in a few days, ending in prolonged sleep. Acute amblyopia has been reported (Kaiser, 1912). The mortality, from various causes, is about 10 to 15 per cent in uncomplicated cases, but may be as high as 37 per cent (Piker and Cohn, 1937), or 50 per cent with trauma. The phenomena are not due to direct narcotic or excitant actions of alcohol, but to encephalopathy, probably chiefly acute cerebral edema (Holitscher, 1908); the cerebrospinal fluid pressure is increased in most cases (Steinbach, 1915). The events are perhaps based on deterioration of the capillaries; petechial hemorrhages are common in the gastric mucosa (E. F. Hirsch, 1916). The other tissues are dehydrated.

Treatment of Delirium Tremens.—Lowering of cerebrospinal pressure by withdrawing 50 to 75 cc. of spinal fluid through a lumbar puncture is reported to be promptly effective, but others advise it only for diagnosis. It may be followed by intravenous injection of 50 to 100 cc. of 50 per cent dextrose solution. Dextrose in orange juice may be given liberally by mouth; also sodium chloride, 2 Gm. every four hours, with liberal water, to combat the general dehydration. High caloric and high vitamin food should be given. Nicotinic acid (0.6 Gm.), and thiamine are reported highly effective. If a direct sedative is needed, paraldehyde (4 to 12 cc., 1 to 3 drachms by mouth or rectum) is generally preferred. Barbiturates are effective in large, but not in ordinary, doses. Active delirium may be allayed by pentobarbital intramuscularly or, if necessary, intravenously. Bromide (1 Gm. every one to four hours) or chloral (not over 1 Gm., at night) may be used against the preliminary restlessness and for continued sedation. Alcohol should never be allowed, nor should morphine be given (K. M. Bowman *et al.*, 1939; Cline and Coleman, 1936; Piker and Cohn, 1937). The attack is likely to continue three to five days even with the best treatment.

Fertility and Fecundity.—These are diminished by high degrees of alcoholism, such as may be entertained experimentally in animals; but unfortunately this is not apparent in human experience, even with advanced habitual drunkards.

In an extensive series on mice, Agnes Bloom employed what she defines as "moderate" doses, but these averaged 1.5 cc. of alcohol per kilogram of body weight, corresponding to nearly half a pint of whisky for man, daily through several generations. With such so-called moderate doses she found some decrease of fecundity and fertility, and some interference of growth, the effects being greater if the alcohol was given to the fathers than for the mothers. The toxicity of alcohol for fetal rats is about the same as for adults; newborn rats are somewhat more resistant (Chesler *et al.*, 1942). Stockard, 1912, found that chronic alcoholism, induced in guinea pigs, either parent, diminishes fertility and causes most of the embryos to die before or shortly after birth. The offspring are often defective, sometimes with gross deformities. This degeneration is transmitted for at least three generations; in fact, it rather increases (1914). Stockard also found (1909) that alcohol and other anesthetics cause various morphologic defects in fish embryos, but this is a different matter.

Bertholet, 1909, reported that the testicles of chronic alcoholics generally show atrophy of the parenchyma, and increase of interstitial tissue, with corresponding decrease and abnormalities of the *spermatozoa*. This would lead to more or less impotence. Ivanow, 1913, reported that the addition of 2 per cent alcohol *in vitro* has practically no effect on the motility of spermatozoa; 12 per cent has little effect; with 15 per cent there is marked impairment. Contact for thirty minutes with 10 per cent alcohol does not hinder their fertilizing action, and the fetus is normal. Arlitt and Wells, 1917, claimed that in white rats the spermatic tissue reacts before any other to the daily administration of alcohol. Arlitt, 1919, also reported that chronic alcoholism induced in rats results in partial or complete sterility in both sexes and in a high mortality of the offspring, and that these defects are transmitted for several generations. With female pigeons, the daily inhalation for one to two hours of nearly paralytic doses of alcohol, for two to four months, reduced the size of the egg yolk materially (Riddle and Bassett, 1916).

Exposure of the ova or spermatozoa of the fish fundulus to alcohol before fertilization produces impaired and abnormal development (Gee, 1917). The concentrations and other conditions of such experiments are so peculiar that they have little meaning for the human problem.

Children of Alcoholic Parents.—The influence of alcoholism of the parents on their offspring is questionable, the data as well as opinions being so contradictory that no definite conclusions may be drawn.

Miss Elderton and Karl Pearson, 1910, in a statistical study covering 3600 school children, could find no real evidence of either physical or mental deterioration (death rate, mean weight and height, general health, mental and visual defects). They concluded that the danger of alcoholic parents lies in the transmission of the hereditary defects which caused the parental alcoholism. O. L. Mohr, 1933, reviewing the more important animal experiments, concluded that most of these have been insufficiently controlled, and that there is no sound evidence of the production of inheritable variations following paternal or maternal alcoholism, even when this exceeds anything that occurs in man. McDowell, 1919, observed lowered efficiency in the solving of maze and similar problems by the nonalcoholic offspring of heavily alcoholized *rats*. Pearl, 1916, found the progeny of *fowl* treated with ethyl or methyl alcohol or ether rather stronger than the controls, although fewer eggs were hatched.

While it is not proved that ordinary alcoholism has a direct influence on the germ plasm, the embryo is exposed to the influence of the alcohol, since this passes readily through the placenta, and exists in the same concentration in the fetal blood as in that of the mother (Nicloux, 1905). Moreover, the children inherit the degeneracy which induces alcoholism in the parents. The statistics of prisons and asylums indicate a tendency to psychic and moral degeneracy among the descendants—epilepsy, idiocy, insanity, disposition to crime and to alcoholism; but it is not decided whether the defective inheritance concerns a degeneration induced in the parent by alcohol, or the degeneration underlying the abuse of alcohol. The latter is more probable (British Royal Commission, 1931).

The **treatment of chronic alcoholism** follows the same principles as with other drug habits. The first essential is the complete ithdrawal of the drug. This may be facilitated by scopolamine. Emetine may be used to establish an adverse conditioned reflex; it is successful in a considerable proportion of patients (F. Lemere, Voegtlin *et al.*, 1942). Suggestion may be useful. The local action of the alcohol may be replaced by capsicum or ginger, the stimulation by beef-tea. Amphetamine sulfate, 30 mg. before breakfast and lunch, helps to make the patient more cheerful and cooperative (M. M. Miller, 1942). Bloomberg, 1939, recommended 5 mg. two or three times daily for some months, to alleviate the craving and so enable the patient to become reestablished. The prospects of cure are better than with morphine or cocaine, but relapses are frequent.

METHYL ALCOHOL

The extensive use of this substance (*Wood Alcohol*, Columbian Spirit) in the arts (as a combustible, anti-freeze, solvent for shellac, and so forth) and as an adulterant of alcoholic beverages and medicines has given rise to numerous cases of poisoning. Over 200 deaths were said to have occurred in the United States in six months, in 1930, from this agent, obtained chiefly from gasoline stations (J.A.M.A., *97:* 1711). The acute symptoms resemble those of ordinary alcoholic intoxication. The main differences are in the stronger local irritation and in the more protracted and more serious after-effects, the coma lasting several days and often terminating in death. An important feature is the frequent occurrence of incurable blindness from retrobulbar neuritis and retinitis. This may occur after taking 10 cc., but the individual susceptibility varies greatly. The effects are produced by the purest samples, and are therefore due chiefly to the methyl alcohol itself, although they may be exaggerated by the impurities (acetone, and so on) which are usually present. Methyl alcohol should never be applied to the body, externally or internally. Its presence in foods and drugs is properly prohibited by law. Protection against the inhalation of its vapors should be enforced in the trades.

Etiology.—The practical seriousness of methyl alcohol poisoning is illustrated by the fact that Buller and Wood found 153 cases of blindness and 122 deaths recorded up to 1904, although the existence of the danger had only been recently recognized. A wholesale poisoning occurred among the inmates of a Berlin municipal lodging house (Stadelmann and Magnus Levy, 1912; Baskerville, 1913, abstracted the cases then in the literature.) Adulterated cologne and bay rum, and the like, have proved toxic when used externally. The "methylated industrial spirit" of the B.P. is ordinary ethyl alcohol mixed with 5 per cent of crude wood alcohol. It has been claimed that mixtures of the two alcohols are more toxic than corresponding doses of either (Pantaleoni, 1927), but this requires confirmation. The *vapor* of methyl alcohol (varnish) is dangerous if ventilation is insufficient (bibliography, J.A.M.A., 1913, *60:* 1237). The inhalation is also highly toxic to animals, the effects agreeing with those in man (Tyson and Schoenberg, 1914; McCord, 1931). Considerable absorption occurs when the air contains 0.2 per cent (A. Loewy and Heide, 1914).

The **general symptoms** begin with *gastro-intestinal* disturbance, excruciating abdominal pain (also after inhalation), general weakness, nausea, vomiting, vertigo, headache. Muscle twitching is common and may increase to convulsive spasms and tonic cramps, especially of the legs. The symptoms of ordinary *alcoholic intoxication* supervene, with delirium, restlessness, unconsciousness, collapse and coma. The pulse is good at first, but later becomes weak. Acidosis is responsible for part of the symptoms (O. Roe, 1943). The plasma CO_2 may fall 10 volumes per cent (W. B. Chew *et al.*, 1946). Dyspnea is agonizing with rapid or deep forced breathing and severe cyanosis. The temperature is subnormal, 35° to 36° C. *Death* is much more frequent than with ethyl alcohol. It occurs in coma, from respiratory paralysis, in a few hours to three days. The *fatal dose* is probably from 100 to 250 cc. *Postmortem examination* shows marked hyperemia and edema of the brain and retina; acute degenerative changes in the gray matter of the brain and spinal cord; and hemorrhages in the cerebral meninges, mucosae, heart and lungs and irritation of the stomach, duodenum, kidneys and bladder (Berner, 1936; Menne, 1938).

Late Symptoms.—Sometimes the symptoms are deferred for several days and then prove rapidly fatal. Delirium may set in after the acute symptoms have subsided. Cystitis is a frequent sequel. The most important sequel, however, is blindness. Deafness may occur.

Optic Injury.—The symptoms are bilateral and consist in scotoma, dimness or total blindness; the pupils are dilated and insensitive to light. The loss of vision may start in a few hours, or be delayed several days; it generally becomes complete; subsequently there is some improvement, which in most cases, however, finally relapses into total blindness or large central scotomas, which are generally permanent (Buller and Wood, 1904; other reports summarized are by Woods, 1913). The ophthalmoscopic findings are at first normal, but later show hyperemia and edema of the fundus and destructive inflammation of the optic nerve or retinal elements or both, followed by their atrophy (Tyson and Schoenberg, 1914). The effective dose varies greatly: 10 cc. has caused blindness in some cases, while 90 cc. has failed to do so in others. Permanent impairment of vision occurs in something like half of all cases of poisoning. The pathologic changes in rabbits are described by Kasava, 1913.

Habituation.—Continued administration to dogs induces tolerance to the normally fatal dosage. The excretion of formate by the urine diminishes with the habituation (Leo, 1927). Fatty degeneration of the liver has been reported.

Cause of the High Toxicity of Methyl Alcohol.—This is not due to impurities, for the purest methyl alcohol is quite as toxic as the impure. The *acute* toxicity of methyl alcohol in animals is about 10 per cent less than that of ethyl alcohol (also for rotifers; Whitney, 1912), but the *subacute* toxicity is markedly greater. This is due to the slower oxidation of methyl alcohol, so that it persists longer in the tissues. The elimination of a single large dose of methyl alcohol extends over a week. Accordingly, while the coma of ethyl alcohol rarely lasts twenty-four hours, that of methyl alcohol may last for three or four days.

This protracted action leads to cumulative effects (Pohl, 1893; Reid Hunt, 1902). Sollmann, 1921, found that *daily* repetition of sublethal doses is more fatal with methyl than with ethyl alcohol. Birch-Hirschfeld demonstrated a similar cumulative action on monkeys. "Tippling" has also been found especially dangerous in man.

Fate.—The protracted and cumulative action is connected with the slow excretion. Voeltz and Dietrich, 1912, found after 2 cc. per kilogram that during two days about 21 per cent was excreted unchanged by the lungs, 3 per cent by the urine, 39 per cent had been burned, and 37 per cent was still in the tissues. Haggard and Greenberg, 1939, found 70 per cent eliminated by the lungs. Nicloux and Placet, 1912, found it present in the blood and brain after five days. The *distribution in the tissues* follows the same principle as for ethyl alcohol; *i. e.*, it is proportional to their water content (Yant and Schrenk, 1937). The *concentration in the blood* is about the same as in the urine (Chabanier and Ibarra-Loring, 1916). The blood concentration in six fatal human cases ranged from 0.114 to 0.238 per cent (Harger, Johnson and Bidwell, 1938).

Formaldehyde and Formic Acid as Intermediate Oxidation Products.—Methanol is oxidized in large part to formaldehyde, and this to formic acid (Pohl, 1893; Keeser, 1931). This is rapidly excreted, but gives rise to some acidosis (O. Roe, 1943). It has been suggested that the formaldehyde or formic acid is responsible for the nerve injury (Keeser); but neutral formates are not especially irritant, and it is improbable that free formaldehyde can exist in irritant concentrations in the neutral or alkaline reaction of the body.

The **treatment of methyl alcohol poisoning** includes gastric lavage and the administration of alkali (Worth Hale, 1924) with dextrose and insulin (B. B. Clark and Gibson, 1933); morphine to allay suffering. W. B. Chew *et al.*, 1946, advocate prompt alkaline treatment by intravenous sodium lactate and oral bicarbonate. Good results are claimed for daily lumbar puncture, even against the blindness, but the prognosis is not good, either as to this or as to fatality. The pressure of the cerebrospinal fluid is not altered, except as it decreases with fall of blood pressure (T. H. B. Bedford, 1946).

Impurities.—The best commercial wood spirit contains about 95 per cent of methyl alcohol; the common varieties, 75 to 90 per cent; some samples, only 35 to 40 per cent. The impurities consist of acetone, methyl acetate, allyl alcohol, aldehyde, empyreumatic products, and the like (Baskerville, 1913). It has been suggested that these are responsible for the peculiar toxicity (Mueller, 1910). Most investigators, however, have found no essential difference between the ordinary and the purest obtainable articles (Hunt, 1902; Buller and Wood, 1904; Sollmann, 1921); nor do any of the impurities produce the characteristic effects (Baskerville, 1913).

Acetone (Dimethyl-Ketone), U.S.P., $CH_3.CO.CH_3$, is used as a solvent for fats, resin, rubber, and so forth. It occurs in wood alcohol and acts similarly to methanol (Morris and Graham, 1927), being somewhat more toxic for acute and less so for delayed fatality (Sklianskaya *et al.*, 1936). Acute poisoning has been reported from its use in synthetic plaster substitutes (R. B. Elliott, 1946).

Its inhalation produces bronchial irritation and stupor, but serious poisoning is rare. It is a rather feeble narcotic, causing considerable dyspnea (Albertoni, 1884) and progressive fall of temperature, respiration and heart rate, proportional to the concentration of the vapor. After inhaling 1 per cent vapor for forty-eight hours, or 5 per cent for five to eight hours, guinea pigs show congestion of the spleen, lungs and kidneys, and pulmonary edema (Specht *et al.*, 1939). Hypodermically (guinea pigs), it is more toxic than methyl alcohol (Rhamy, 1912). It is excreted mainly by the lungs.

Acetoin (methyl acetyl carbinol), $CH_3.CH(OH).COCH_3$, produces inebriation resembling that of alcohol. It is about a fourth more potent as regards respiratory failure (L. A. Greenberg, 1943).

Butanone (methyl ethyl ketone) was studied by Patty *et al.*, 1935, as regards the toxicity of its vapor.

Higher Alcohols.—In acute intoxication, the toxicity of the alcohols increases with the size of the molecule as illustrated by the acutely lethal dose for cats (Macht, 1920): Taking methyl alcohol as 1, ethyl as 1.2; propyl

2.95; butyl, 19.7; amyl, 39. This (*Richardson's law*, 1869) applies also to the individual tissues; sensory and motor nerves, ciliated epithelium, muscle, ova, heart (Kuno, 1913). The toxicity of the alcohols for rabbits was studied by Munch and Schwartze, 1922; for paramecium, by Bills, 1923. The toxicity of aliphatic alcohols in relation to their constitution and fate is reviewed by W. F. von Oettingen, 1943.

Iso-propyl alcohol, $CH_3.CHOH.CH_3$, is used as a solvent and substitute for ethyl alcohol. It resembles this closely in action, local and general. It is used, best in full strength, as *antiseptic* for metal instruments, with the advantages over 70 per cent ethyl alcohol that it is more effective, penetrates better, is more rust-resistant, and less irritant to the skin. Neither is effective against spores. It boils between 71° and 83° C. and mixes freely with water (N.N.R.).

The odor and taste are disagreeable, so that it is not suitable for internal use (H. C. Morris and Dragstedt, 1946).

Its *acute narcotic potency* is about twice that of ethyl alcohol (A. J. Lehman *et al.*, 1944). No instances of eye injury have been reported. It is oxidized and disappears from the blood stream at about the same rate as does ethyl alcohol (Bijlsma, 1928; Fuller and Hunter, 1927). Insulin and water diuresis, with or without dextrose, have no effect on the metabolism of iso-propyl alcohol (A. J. Lehman, 1946). When 0.1 to 20 Gm., as 40 per cent solution, are administered to man, it appears in the urine and alveolar air, partly as acetone (H. Kemal, 1927). *Continued administration* to rats, as 5 per cent in the drinking water over nine months, averaging 1.87 cc. per Kg. daily, rendered them somewhat sluggish and stupid, but the mortality rate was about that of the controls (L. L. Boughton, 1944); 2.5 per cent continued for two generations had no effect on reproduction or offspring. Dogs *developed some tolerance* with more rapid fall of the blood level, in contrast to ethyl alcohol (A. J. Lehmann *et al.*, 1945).

The actions of **propyl alcohol,** $CH_3.CH_2.CH_2OH$, were studied especially by Macht, 1921, and Grant, 1923. **N-butyl alcohol** (*butanol*), $CH_3(CH_2)_3OH$, is reported to produce corneal lesions in industrial workers, not in animals (Cogan and Grant, 1945).

Allyl alcohol, $CH_2{:}CH.CH_2OH$, occurs in commercial methyl alcohol to the extent of about 0.2 to 0.5 per cent. It produces gastro-intestinal irritation, convulsions and coma, but is apparently much less toxic than methyl alcohol (Atkinson, 1924). However, McComb, 1932, found it highly toxic to various animals.

Iso-amyl alcohol, $C_5H_{11}OH$, the main constituent of "fusel oil," is more violent than ethyl alcohol in its acute and subacute actions (Salant, 1909) and the after-effects are more pronounced, but its admixture up to 1 per cent produces little difference in acute alcoholic intoxication (Baer, 1898). The toxicity of the amyl alcohols, their ketones and metabolites, is reported by H. W. Haggard *et al.*, 1945. **Amyl acetate,** the so-called "banana oil" used as a solvent in cellulose lacquers, when inhaled irritates the nose and produces headache, confusion, throbbing, palpitation, nausea, gastric derangements, but workmen soon acquire considerable tolerance. Exposure of guinea pigs to 0.2 per cent vapor of secondary amyl acetate shows only conjunctival and nasal irritation; 1 per cent causes narcosis, coma and death in five hours of exposure. The brain, lungs, liver and kidneys are congested (Patty *et al.*, 1936). *Cyclohexanol acetate,* which is used similarly, causes the same effects.

Caprylic alcohol, octyl alcohol, $C_8H_{17}OH$, is used as anti-foaming agent in various industries. No poisonous effects on the workers have been reported. In animals, it acts as a mild local anesthetic. Intravenous injection lowers the blood pressure (Clerc, Stern and Paris, 1934). Its hemolytic potency is fifty times that of ethyl alcohol (P. L. McLain, 1939).

VOLATILE ANESTHETICS

Ether, chloroform and other volatile hydrocarbons are employed mainly for producing surgical anesthesia. General anesthesia is conceived clinically as reversible paralysis of the central nervous system; specifically, loss of consciousness, pain and voluntary movements, without serious impairment of respiration and circulation (M. Kochmann). These hydrocarbons depress successively the psychic centers, then probably the basal ganglia and cerebellum; then the spinal reflexes, first the sensory and then the motor functions of the cord, probably from below upward; and finally the medullary centers. The most highly evolved functions are affected first. Chloroform also has a direct depressant effect on the cardiac muscle and is generally more dangerous. Locally, they act as irritants. For surgical anesthesia it is aimed to produce unconsciousness, preferably with muscular relaxation, with the minimum of danger, unpleasantness and after-effects. Volatile anesthetics have advantages over dissolved anesthetics in that their rapid absorption and elimination by the lungs makes it possible to adjust their action more quickly and more accurately to the condition of the patient. They require skillful attention, however, and are apt to interfere more or less with the oxygen supply. These disadvantages may be diminished by the preliminary administration of sedatives. The relative advantages and disadvantages of general, local and spinal anesthesia involve other considerations which lie largely outside pharmacology.

Discovery of Surgical Anesthesia.—The use of narcotics for dulling the pain of operations dates back to antiquity: however, the discovery of the means to achieve complete and safe anesthesia is an accomplishment of the nineteenth century (1842 to 1847). The credit must be divided among several investigators: Humphry Davy for the definite suggestion; C. W. Long for the independent discovery, but inadequate publication of ether anesthesia; Horace Wells for the successful use and publication of nitrous oxide; Jackson and Morton for the successful public demonstration of etherization; Flourens and Simpson for the introduction of chloroform (Claude Bernard, Anésthesie).

The Egyptians probably employed narcotics. The Assyrians are said to have strangled children before circumcision, producing anesthesia by the aid of CO_2. This method was revived by Valverdi in Italy early in the seventeenth century. The Chinese used hashish. All kinds of narcotics were given during the middle ages, especially opium and drugs containing hyoscine (such as the legendary "mandrake," Mandragora officinalis). "Scopolamine-morphine-anesthesia" is an interesting reversion to this ancient method, which became obsolete when the vastly superior inhalation anesthesia was discovered. Sir Humphry Davy in 1799 announced the anesthetic properties of nitrous oxide (laughing gas) and suggested: "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place." The suggestion was not acted upon at the time. The production of insensibility by the inhalation of ether had also been observed repeatedly in accidents and experiments; Charles T. Jackson, a chemist of Boston, etherized himself into unconsciousness, in the winter of 1841 to 1842, and thereby conceived the idea of ether anesthesia. He did not apply it further, but discussed it with various persons, among others with Morton. Dr. Crawford W. Long, of Jefferson, Ga., who had witnessed the effects of ether inhalation in "ether parties," was the first, in 1842, to perform an actual surgical operation under ether anesthesia. Interesting accounts of this have been given by his daughters, Mrs. E. L. Harper (Wisconsin Medical Journal, Sept., 1934) and Frances Long Taylor (Marquette Medical Review, March, 1937). In 1845 he administered ether in delivering his own child, and this was also the first recorded use of anesthesia in childbirth (Boland, 1936). However, he neglected adequate publication of his discovery of anesthesia until after this had been discovered independently by others. Dr. Horace Wells, a dentist of Hartford, Conn., witnessed an exhibition of "laughing gas" in a public lecture by Colton in December, 1844. He noticed that one of the subjects was insensible to pain; acting on this hint, he had a tooth extracted under its influence on the next day. The operation was a complete success. He introduced the gas into general dental practice in Hartford, and gave the matter wide publicity, without reservation. The intoxicant action of ether being well known, he tried this with Dr. Marcy of New York, early in 1845, but thought it inferior to the gas. There can be no question that Wells discovered anesthesia independently, and that he introduced it successfully into practice; he seems to have been the first to realize fully the importance of the discovery. Unfortunately, an attempted public demonstration in Boston in January, 1845, partly failed and was met with ridicule. The successful demonstration of ether by Morton threw nitrous oxide completely in the shade for many years. Wells was greatly disappointed, became insane and committed suicide (Truman Smith, 1858, "An Examination of the Question of Anesthesia"). The use of the gas was revived about 1863 by Colton (whose demonstration had started Wells), and by 1868 it was extensively used in dentistry. It has since been reintroduced into major surgery, and has thus vindicated the claims of Wells. William T. G. Morton, a dentist of Boston, and a former friend of Wells and Jackson, probably received inspiration from both. It is said that after hearing about Wells' discovery, Morton consulted Jackson about the manufacture of nitrous oxide, and Jackson suggested ether as more convenient. Morton seems to have started successful experiments with ether anesthesia in September, 1846. In October, 1846, he gave a perfect demonstration at an operation by Dr. J. C. Warren at Massachusetts General Hospital. The complete success of this operation achieved the introduction of anesthesia into surgery. Morton obtained a patent in November, 1846. This step, and the methods he was said to have employed to obtain it, raised much opposition. His life was embittered by the controversies, and he died of apoplexy. Jackson, the third party to the unfortunate contention for priority, also became insane. The use of anesthetics spread rapidly, and related substances were tried: chloroform was used on animals by Flourens in 1847, and in the same year, on the independent suggestion of McWaldie and Duncan, by Simpson of Edinburgh, on man (Gilmour, 1934). Flourens in the same year also called attention to ethyl chloride. It was used surgically by Heyfelder in the next year, but was then neglected till 1895. The first fundamental scientific work on the action of anesthetics was published by Snow, 1858. Ether was discovered by Valerius Cordus, 1540; chloroform, independently by Liebig, Soubeiran and Guthrie, 1831. The clinical use of *hypothermia* ("*crymotherapy*") for producing amnesia and general anesthesia is reviewed by L. W. Smith, 1942. The structural alterations of the brain in *concussion* anesthesia were studied by Windle and Groat, 1944.

Stages of Anesthesia.—The main actions of alcohol, ether, chloroform, chloral and the numerous other hydrocarbon or lipolytic narcotics are very similar; but they show practically important differences in severity, rapidity, duration and sequels. The successive effects may be divided into "stages." Hewitt, *f. i.*, classifies these as (1) analgesia, (2) light anesthesia, (3) deep anesthesia, and (4) bulbar paralysis. Since the effects pass without abrupt transition from one stage to the other, all classifications are arbitrary. In the following, they will be divided merely into the preanesthetic, anesthetic and paralytic stages. In surgical practice, the normal course of anesthesia is generally "complicated" by asphyxial phenomena, traumatic reflexes, hemorrhage, and so forth.

Preanesthetic Stage.—This sets in with a comfortable *feeling of warmth*, spreading over the whole body, but soon associated with a distressing *sensation of suffocation*, if the access of air is limited, as in the "closed" methods. The *local effects* make themselves felt by prickling and smarting of the nose, throat and conjunctiva, with hypersecretion of mucus, tears and saliva. The suffocation, as well as the direct effects of the anesthetics, results in more or less *excitement and struggling*, sometimes convulsions, especially in hysterical patients. The *reflexes* are at first rather exaggerated, later somewhat depressed and less purposive. Tonic muscular *spasm*, general or of the jaws, glottis or respiration, may occur. Sensation becomes impaired after the first few inhalations, first with disturbance of the special senses, then poor localization and diminished acuity of touch and pain. Stimulation may evoke responses, although it is not felt. This "*primary analgesia*," while the patient is still conscious, may be used for short operations, especially under chloroform and nitrous oxide.

The mind becomes *confused*, with hallucinations (noises, and so on), sensation of stiffness and want of muscular control. The patient may lose self-control and indulge in loud incoherent talking, laughing, singing, and the like, passing gradually into unintelligible muttering. These initial excitement symptoms vary in duration and intensity in different patients. Alcoholics may exhibit violent delirium and even mania. *Vomiting* (probably central), retching and coughing may occur. The *face* is flushed; the *pupils* are at first dilated, then gradually constricted; the *pulse* is rapid; the blood pressure, increased; the *respiration*, somewhat quickened and at times irregular, sometimes suspended if the vapor is too strong.

Ether as Intoxicant.—The resemblance of the earlier effects of ether to those of alcohol led to its use as an intoxicant. This is said to have been common in Ireland toward the end of the last century. A teaspoon to a tablespoonful produces effects similar to those of whisky, but they are produced, and pass off, more promptly than with alcohol (discussion and literature, J.A.M.A., *64:* 168, 1915).

The *anesthetic stage*, which it is aimed to produce and maintain, is characterized by complete paralysis of the brain and of the motor reflex centers of the cord, and usually some depression of the medullary centers. *Consciousness, sensation and most reflexes are lost*—the *corneal reflex* being among the last. Consequently the *muscles are lax*. The smooth muscles are not usually affected, but there is sometimes a relaxation of the sphincters. The pulse is full and soft, the rate rather slow with chloroform, slightly faster than normal with ether; the *blood pressure* is lowered by chloroform, normal or rather raised by ether. The *respiration* is regular and deep, often softly snoring or stertorous; rather rapid with ether. The *temperature* falls in consequence of the diminished muscular activity and increased heat loss. The *pupils* are somewhat small and respond sluggishly to light. The *face* is pale with chloroform, often cyanotic with ether.

The medullary depression does not reach a dangerous degree if the administration is carefully done. But with *prolonged anesthesia* the pulse tends to become progressively weaker, the respiration more shallow, and the temperature lower—it may fall as much as 5° C., through paralysis of the function of temperature regulation.

The *paralytic stage* involves progressive paralysis of the medulla. This stage must be carefully guarded against. All *reflexes* disappear. The *respiration* becomes shallow, irregular, labored and then ceases. The *skin* is cold and pale, and covered with the clammy sweat of the "agony." The *pupils* are widely dilated. The *pulse* becomes slow and weak, and ceases normally after the respiration.

Recovery of Patient from Normal Anesthesia.—The rapidity of the recovery is inverse to the duration of the administration. The first change after the withdrawal is usually in the respiration, which becomes quieter and less stertorous. Then the lid reflex and deglutition movements reappear. The pupils generally grow smaller, but dilate easily. The breathing may be disturbed by swallowing, coughing, retching and actual vomiting, usually just before consciousness returns. This is commonly succeeded by sleep, lasting several hours. Thirst and gastritis persist for some time.

Individual Functions.—The proper administration of anesthetics requires a detailed knowledge of their effects on the important individual functions in the successive stages.

The **reflexes** are progressively suppressed; first those which require consciousness, then the spinal muscular reflexes, and last the medullary reflexes of the respiration and circulation. The gradual abolition of all spinal reflexes by ether and chloroform produces complete muscular relaxation in the anesthetic stage—an important surgical advantage over nitrous oxide or local anesthesia. The relaxation and reflexes are also valuable in judging the depth of the anesthesia, for the reflexes vary with remarkable uniformity according to the concentration of the anesthetic in the blood and even according to the concentration in the air. There are, however, rare exceptions. No initial stimulation of reflex excitability is noticeable (Mann, 1918). The reflexes disappear in a rather *definite order;* but this is not the same for chloroform and ether, indicating that their actions are not strictly alike (Storm van Leeuwen, 1916). In recovery, the reflexes tend to return in inverse order, but not absolutely so (Cetveriko, 1928). There is also some variation with individuals, so that judgment of the degree of anesthesia should be based on a composite of various reflexes. Those which are especially utilized practically are the laryngeal and pharyngeal (gagging), conjunctival, pupillary, and muscle tonus. Among the last to disappear are the rectal, vesical, peritoneal and genital. The patellar reflex persists late. The movements of paralysis agitans cease during anesthesia as they do in sleep.

Appraisal of Depth of Anesthesia in Animals.—The criteria were reviewed by Girndt, 1932. He favors the composite suggested by Magnus and Versteeg.

The Sensory Component Is Depressed before the Motor Component.—In the early stages sensation is blunted; motion is unimpaired or indeed increased. The psychical condition is similar to that from alcohol, but the facilitation of motor processes is early obscured by the sensory depression (Kraepelin, 1892). In decapitated cats, the spinal cord stimulation by moderate doses of aliphatic narcotics results in convulsive twitching (Blume, 1926). In the deeper stages, the sensory cells of the spinal cord are paralyzed before the motor cells: if chloroform is restricted to the upper half of the cord, so that this will not react to reflexes from the upper extremities, it will still respond to impulses from the unpoisoned sensory cells of the lower cord (Bernstein). The response to direct stimulation of the cord disappears first from the sensory posterior columns (Flourens, 1847). Eventually, the motor cells also become inexcitable.

The *cerebral motor cortex* is depressed, but loses its excitability only in deep anesthesia (Hitzig, 1873; ether, Dandy, 1927; chloroform, Chauchard and Chauchard, 1927).

Action Potentials of the Cerebral Cortex.—Ether, chloroform and alcohol first increase the spontaneous electrical fluctuations (alpha waves) as in sleep, but these become damped as the narcosis progresses. In anesthesia they are greatly weakened without much change of frequency. Finally they are abolished, first in the cerebrum, then in the cord and last in the medulla. The response to inhibitory stimuli, *f. i.*, of the sciatic, is abolished rather early, apparently by blocking the afferent approach. In waking, the waves reappear in the reverse order (H. Berger, 1934, human; Hasama, 1935, rabbit; Derbyshire *et al.*, 1936, cat; Bremer, 1935). The *p*H of the cerebral cortex falls and recovers closely parallel to the diminution of electrical activity (W. S. McCulloch and Dusser de Barenne, 1939). *Pre- and postanesthetic excitement* is due partly to stimulation of certain cerebral regions, partly to functional disharmony with synchronous excitation of some parts and depression of others. The wave frequency changes are more or less characteristic for each anesthetic agent, but these tend to fall into two groups (H. K. Beecher and McDonough, 1939): *Avertin narcosis* in human subjects decreases the rate and duration of the waves, but they remain clearly defined. *Barbiturate narcosis* (by pentobarbital, pernocton or evipal) produces the large regular waves characteristic of normal sleep, but if the dosage is increased to deep anesthesia, the waves are depressed as with ether. *Asphyxia* damps the waves, similar to deep avertin or pentobarbital narcosis.

Respiration.—This is influenced, not only by the direct action of the anesthetic, but also by the patency of the respiratory channels; local and distant reflexes; the state of the circulation, and so forth. *In the early stages*, if local irritation is avoided, the respiration is generally somewhat deeper and quicker from stimulation of the respiratory center. More commonly it is likely to be irregular, especially if the administration is started abruptly, on account of the struggling, choking sensation and local irritation. The latter may produce temporary expiratory stoppage by a trigeminal reflex (Kretschmer, 1870), but in man this reflex is not usually so strong or lasting. The "choking" is especially pronounced with ether. Reflex closure of the larynx may produce asphyxia under chloroform (Bernard). With chloroform, spasmodic arrest of respiration may also sometimes occur, especially in vigorous subjects, and is probably a common cause of the early deaths. This is less likely to occur if dilute vapors are employed.

As the patient passes into anesthesia, the breathing becomes regular and noisy; with ether, the depth and rate may at first be increased; with chloroform they are decreased, partly by the low blood pressure. The respiration is mainly diaphragmatic. The snorting and the louder "stertor" are generally produced by the vibration of the tongue against the pharyngeal wall. "Stridor" is laryngeal, due to paralysis or spasm of the vocal cords or obstruction of the glottis by mucus. As anesthesia deepens, increase of concentration usually makes the respiration temporarily deeper, quicker and more stertorous, and *vice versa.* Cheyne-Stokes respiration is not uncommon with chloroform, but it is exceptional with ether, because the CO_2 tension is high.

Reflex respiratory changes occur even during full anesthesia, but are most marked if the anesthesia is light. The respiration is usually stimulated by the operative procedures, which may provoke coughing, deglutition, retching, stertor or spasmodic inspiratory or expiratory arrest. Operations during partial anesthesia are therefore dangerous.

With the approach of the paralytic stage, the respiration becomes more stertorous (softly snoring with chloroform), irregular, dyspneic, gasping and finally stops, gradually or suddenly, often with some postmortem gasps. Paralysis of the respiratory center is the usual mode of death in deep anesthesia. Chloroform has a more pronounced paralytic action than ether; the paralysis may also be due to low blood pressure.

Reflex Inhibition of Respiration.—Deep etherization depresses or abolishes all augmentory reflexes, but intensifies those that produce inhibition. For instance, stimulation of the afferent vagus or superior laryngeal fibers causes only short arrest of the respiration in normal animals. As etherization deepens, the arrest becomes longer. With deep anesthesia, not much beyond the surgical limit, the arrest is so long that the resulting asphyxia kills the heart (F. C. Mann, 1918).

The *factors in the respiratory effects* are classified by Y. Henderson and Scarbrough, 1910, as follows:

1. *The Threshold of Excitability for Carbon Dioxide.*—This is *elevated* (*i. e.*, the excitability is depressed) by morphine, chloroform and deep etherization. It is *lowered* by light etherization, by the acidosis of deficient oxygenation, and by fear.

2. *The Carbon Dioxide Content of the Blood.*—This acts as a stimulant to respiration. It varies inversely as the respiratory ventilation.

3. *The Threshold of Excitability for Afferent Impulses.*—This is *raised* (*i. e.*, respiration is depressed) by deficiency of carbon dioxide (acapnia); and by morphine, chloroform and ether. It is *lowered* by fear.

4. *The intensity of afferent impulses,* especially pain and psychic impressions.

5. *Inhibitory cerebral impulses,* such as the fortitude of the patient.

The several anesthetics act differently on these factors: *morphine* raises the threshold for carbon dioxide, but has less effect on the threshold for afferent impulses. It quiets excitement. *Chloroform* raises the threshold more for afferent impulses than for carbon dioxide. *Ether* may lower the carbon dioxide threshold, while the afferent threshold may be elevated. Hence, ether tends to increase respiration (Fonteyne, 1906), so much so that in dogs it may cause fatal acapnia (Y. Henderson, 1925). Most ether fatalities occur in the preanesthetic stage, the respiration almost always failing before the heart (Cunningham and Anderson, 1908). This tendency may be neutralized by morphine. The *respiratory excitement* during the early stages of anesthesia has a similar tendency; it lowers the carbon dioxide content of the blood and thus tends to subsequent failure of respiration. Good surgical anesthesia obviates the development of acapnia by preventing pain hyperpnea.

Excessively deep anesthesia paralyzes respiration by raising the threshold of the respiratory center, and by diminishing the production of CO_2. The paralysis is essentially central, although a curare action on the phrenic nerves may play a minor part (Githens and Meltzer, 1914).

Anesthesia before pain prevents acapnia by lessening the afferent hyperpneic impulses. The induction of *anesthesia after pain* is more dangerous, because the lowered excitability during hyperpnea is liable to lead to acapnia (Henderson, 1910). The acapnia also damages the heart, so that it succumbs more easily to chloroform (Cathcart and Clark, 1913).

Stoppage of respiration is therefore most likely to occur with uneven anesthesia (Henderson, 1911).

Irritation of Respiratory Passages.—Ether and, to a less degree, chloroform produce irritation, with reflex phenomena, increased flow of saliva and mucus, and sometimes inflammatory after-effects. The hypersecretion is especially marked with ether; chloroform produces only a slight increase during induction, and practical arrest during full anesthesia. Emphysema, bronchitis and advanced tuberculosis are therefore special contraindications to ether. The increased flow of saliva and the anesthesia of the larynx may lead to *aspiration pneumonia* (Hoelscher, 1898). Pneumonia may also be due to direct irritation, to chilling, to lowered resistance, and to hemorrhagic emboli; it is not known which has the larger share. It is much more common with ether than with the other anesthetics. It has been attributed to *impurities,* especially aldehydes and peroxides (Bruns, 1895; Smith, 1913), but this has not been established. Excessive mucous secretion may also produce acute suffocation by "inundation." The *tongue* during anesthesia is liable to fall against and close the glottis. These accidents are largely obviated by proper position of the head.

Coughing, retching and vomiting sometimes occur immediately after starting the administration; or later, during imperfect full anesthesia, especially with ether, being partly due to the swallowing of mucus. Their occurrence indicates that the anesthesia should be deepened. The approach of vomiting is heralded by swallowing movements. If it cannot be averted, the head should be turned to the side and the opposite shoulder raised.

The *viscosity of mucus* (tracheal and frog's esophagus) is greatly increased by ether inhalation. Chloroform, ethylene and nitrous oxide do not have this effect (Lucas and Henderson, 1936).

Salivary Secretion.—The flow from Stensen's duct in dogs is increased two to five times during induction of and recovery from ether, chloroform and cyclopentane; not with ethylene, nitrous oxide or barbiturates. The salivation of ether induction is a reflex from the upper respiratory mucous membranes, for it does not occur if these are cocainized, or if the ether is administered by trachea or intravenously. During full anesthesia, the salivary secretion is arrested by all these agents, but pilocarpine provokes a copious flow (B. H. Robbins, 1935).

Ciliary Motion.—In the mammalian trachea and bronchioles this is depressed by ether, chloroform and ethyl chloride (Lucas, 1934; Sollmann and Gilbert, 1937; A. M. Ernst, 1938). Ethylene stimulates at first, then depresses (Lucas). With ether, the motion is further impaired by the increased viscosity of the mucus (Lucas and Henderson, 1936). In frog's esophagus, alcohol and ether, as well as ethylene, stimulate before they depress. Chloroform and chloral give pure depression (Lucas, 1934).

Bronchial Muscle.—Excised tracheal muscle is relaxed by ether, constricted by chloroform, in vapor concentrations such as occur in anesthesia (Trendelenburg, 1912). In intact animals, however, chloroform produces slight dilatation (Dixon and Brodie). In excised lung (guinea pig), temporary dilatation is produced by ether, chloroform and urethane (Baehr and Pick, 1913). Sollmann and Gilbert, 1937, found the effects rather slight with fresh microscopic sections. By the same method, Adriani and Rovenstine, 1941, observed some *dilatation* with chloroform, ether and divinyl ether; *constriction* (antagonized by atropine) with cyclopropane, amytal and other barbiturates; practically no effect with ethylene, nitrous oxide and paraldehyde. *Anaphylactic reactions* can occur during ether anesthesia, clinically and experimentally (L. M. Quill, 1937).

Pneumococcus Infection.—The resistance of highly immunized rabbits is inhibited during ether anesthesia (and alcohol stupor), the immigration of leukocytes being prevented by alteration of the capillaries. The phagocytic activity of the leukocytes is not inhibited (Pickrell, 1938). On the other hand, alcohol or ether narcosis of rabbits tends more or less to inhibit the inflammatory response, the hyperemia, edema and leukocytosis, to *bacterial and chemical irritants* (Cressman and Rigdon, 1939).

Circulation.—This reacts differently to the various anesthetics, directly and indirectly. Asphyxial rise of blood pressure tends to occur when the air exchange is impeded, as in rebreathing methods, including nitrous oxide and the "closed" ether administration, and if the percentage of oxygen in gases is too greatly restricted. Otherwise, the circulation is not greatly altered in anesthesia by ether, ethylene, cyclopropane and nitrous oxide with oxygen. Chloroform, however, causes marked and progressive fall of pressure, partly cardiac and partly vascular; and sensitization to ventricular fibrillation by the epinephrine. Cyclopropane also sensitizes to fibrillation, and may produce this directly if the concentration is too high (review, W. J. Meek, 1941). Chloroform death may occur through cardiac arrest, sometimes reflexly, but generally because the poisoned heart is unable to withstand the strain of the impaired respiration.

Electrocardiographic Phenomena in Surgical Anesthesia.—Four-fifths of 109 patients under the various anesthesias in current use developed some disturbance, usually of rhythm, especially sinus arrhythmia and extra systoles, also variations of amplitude, sometimes extreme ventricular irregularity, rarely complete heart block. Chloroform had the highest incidence, procaine the lowest. There was no constant relation between the arrhythmias and the depth of anesthesia (Kurtz, Bennett and Shapiro, 1936). In *dogs*, ether and cyclopropane tend to reverse the T wave and often cause transient arrhythmias. Amytal had no effect (Betlach, 1937). Cyclopropane is particularly liable to produce ventricular fibrillation.

Ether on Circulation.—*In the early stages*, the pulse rate and blood pressure are increased by the reflexes, excitement and incipient asphyxia. *During anesthesia*, the effects are similar to those of alcohol, stimulant rather than depressant: the cutaneous and cerebral vessels are dilated (also with chloroform, Berezin, 1916), the intestinal constricted (Derouaux, 1909), the pulse rate is increased to 80 to 110, and the blood pressure is practically unchanged, or somewhat above normal in man (Blauel, 1901). The face is reddened. The pressure in the pulmonary artery rises even if the carotid pressure remains unchanged (Wood, 1911). There is generally some venous congestion, especially with the "closed" methods (asphyxia). The threshold to vagus stimulation is raised (Jackson and Ewing, 1914), chiefly by an action on the vagus ganglia. The femoral blood flow in dogs anesthetized by ether is two or three times that under local anesthesia. The mechanism is not clear (J. F. Herrick *et al.*, 1932).

These indifferent or favorable actions on the circulation persist through the stage of surgical anesthesia, even if this is prolonged for hours. *In the paralytic stage*, the vasomotor center is gradually depressed: the pressure falls slowly, the face becomes pale, while the heart remains practically normal even when the respiration ceases. It can therefore usually be revived effectively by prompt artificial respiration. Fatty feeble hearts, however, may be affected more severely. The vascular effects are central; the cardiac changes are mainly the indirect results of the vascular disturbance, the heart muscle (Bock) remaining unchanged. Concentrations of ether which injure the heart directly can be reached only in perfusions.

Toxic Circulatory Effects and Concentration in Blood.—These were investigated on cats by Schram *et al.*, 1916. With normal cats, concentrations of 0.13 to 0.14 per cent of ether in the blood lower the blood pressure considerably by action on the vasomotor and vagus centers; but the heart muscle is not affected by this concentration. Even with the fatal concentration (0.17 per cent), the heart is scarcely damaged, although the circulation is depressed before death. If artificial respiration is performed, cardiac arrest occurs with 0.25 per cent of ether in the blood. This also is not essentially due to direct injury of the heart muscle; for by dividing the vagi, the minimal fatal concentration becomes 0.31 per cent. If low blood pressure is excluded (by the Starling arrangement), it becomes 0.44 per cent; if the nutrition of the heart is maintained (by Langendorff perfusion), the concentration rises to 0.553 per cent before the heart is arrested.

Asphyxial Effects on the Circulation.—Slight mechanical interference with the respiration rather improves the respiratory movements and the circulation by stimulating the medullary centers. Severer grades produce venous congestion and extensive bleeding from severed vessels. Profound asphyxia leads to extreme cardiac dilatation by paralysis of the vasomotor center and heart.

In light ether anesthesia, 12 to 16 per cent of CO_2 in the air raises the blood pressure, but slows and weakens the heart. These actions are much less pronounced in deep anesthesia (Cathcart and Clark, 1913). The secretion of *cerebrospinal fluid* is increased by the anesthetics and CO_2 (Dixon and Halliburton, 1913).

Heart Rate and Blood Pressure.—In light anesthesia, as in normal individuals (Marey, 1860), the heart rate tends to vary inversely to the blood pressure; *i. e.*, as the blood pressure falls, the heart rate quickens, a response involving the accelerator innervation. In deep ether anesthesia, however, and with anoxemia or profound anemia of the medulla, this coordination fails, so that the heart rate decreases with further fall of pressure.

Vasomotor Center.—Anesthetic doses of ether produce either no direct effect, or moderate stimulation. The stimulation is probably largely asphyxial, from respiratory depression (Pilcher and Sollmann, 1915). In decerebrate cats, ether, chloroform and similar anesthetics depressed the excitability of the vasomotor center to CO_2 (van Esveld, 1930).

Anesthetics on vasodepressor reflexes (from carotid sinus and aortic arch) are diminished or suppressed by ether, chloroform, chloral and barbiturates. Chloralose and urethane have little if any effect on any of the carotid sinus reflexes, cardiac and respiratory as well as vasomotor (Heymans *et al.*, 1931, 1933).

Narcotics on Circulation of Pia Mater.—In cats, ether dilates the pial arteries and veins, and *increases* the cerebrospinal fluid pressure and systemic blood pressure. Chloroform, barbital and amytal dilate the pial vessels and increase the cerebrospinal pressure, but lower the blood pressure. Avertin *diminishes* the pial pressure, and the cerebrospinal and the general blood pressure. Morphine (to 2.2 mg. per Kg.) leaves these pressures unchanged (Finesinger and Cobb, 1935). The vessels of the *cerebral cortex* are dilated by ether anesthesia more than in barbiturate narcosis; but the *hypothalamic vessels*, especially those of the nuclei, are less dilated with ether than with barbiturate (A. Laidlaw and Kennard, 1940; India ink injection of monkeys).

Anesthetics in "Shock."—In partial shock, ether anesthesia depresses the circulation more profoundly. The use of nitrous oxide-oxygen mixture (3:1) does not produce this depression. In any case, deep anesthesia, and rebreathing methods, should be avoided in shock (Cannon, 1919).

Plasma Volume.—Etherizing of dogs for one to two hours reduces their plasma volume by about 12 per cent; prolonging the inhalation does not result in farther fall unless the depth of the anesthesia is also increased. Restoration to normal or above occurs within two or three hours after discontinuing the inhalation (McAllister, 1938). The interstitial tissue fluid is also decreased by ether anesthesia, much less by nitrous oxide and cyclopropane. Barbiturates increase the plasma volume without much effect on interstitial fluid (D. D. Bonneycastle, 1942). The *water absorption by frogs* during anesthesia with various narcotics varies directly as the anesthetic potency (Mild and Serritella, 1934). The increase with alcohol is additive with that of pituitrin administration (F. Brunn, 1943).

Cardiac irregularities in ether anesthesia occur especially during the induction (I. G. W. Hill, 1932). Various electrocardiogram changes have been described, especially in the T wave, but have little if any significance. Blocks and ectopic beats are rare in light anesthesia, but may appear as this is deepened. They disappear rapidly on removing the ether. Ventricular tachycardia and fibrillation are rare with ether alone; and considerably larger doses of epinephrine are required to produce fibrillation with ether than with chloroform or cyclopropane. Ether-epinephrine syncope does not occur clinically (review, W. J. Meek, 1941). *Perfusion of excised frog heart* with 0.5 per cent of ether in Ringer solution causes marked depression at first; on continuing the perfusion, the activity returns to normal (Cattell, 1927).

Cardiac Nerves.—The excitability of the vagus trunk is not diminished in anesthesia (Berline and Chauchard, 1925), although the concentration of the anesthetic in the nerve is relatively high (Nicloux). The cat is peculiar in that the heart becomes nonresponsive to vagus stimulation under full ether anesthesia. The action appears to be on the ganglia, for acetylcholine still causes slowing, while nicotine does not. Accelerator stimulation is not affected (Kobacker and Rigler, 1929). In dogs, ether overcomes the morphine bradycardia, apparently by depression of the vagus system, not by sympathetic stimulation (B. H. Robbins *et al.*, 1939).

The effects of chloroform on the circulation are much more serious than those of ether. Even in smooth anesthesia the pressure falls markedly by central vasomotor depression. Slight faults, especially early in the administration, may produce sudden permanent arrest of the heart. "A.C.E. Mixture" and ethyl chloride act similarly.

In normal chloroform anesthesia, with carefully graduated administration, the pulse and blood pressure in the *preanesthetic stage* are somewhat irregular, but generally increased, and the face is flushed, similarly to ether. *As anesthesia* is reached, or shortly after, *the blood pressure declines progressively* (Lenz, 1853; English Chloroform Commission; Blauel in man); in an hour it may have fallen to one-half, in two and one-half hours to one-third, the normal level (Rosenfeld, 1896). This fall of pressure is primarily due to depression of the vasomotor center: The vessels are dilated, but constrict on stimulation of their nerves (Scheinesson, 1869). The depression of the center can be shown directly by the perfusion method (Sollmann and Pilcher, 1911). The dilatation involves mainly the splanchnic area (oncometer, Embley, 1902; increase of blood flow, Pick, 1899). The skin becomes pale and cold. The cerebral vessels constrict, the pulse is soft and slow but regular, the heart beating efficiently when the vasomotor paralysis is complete (no response to asphyxia, Knoll, 1878). The respiration also remains regular and efficient. The vasomotor depression is not necessarily harmful to the patient, unless it be excessive or prolonged.

With *prolonged anesthesia,* or with the approach of the paralytic stage, the heart is injured more or less by the direct action of the chloroform, as well as by the low blood pressure and asphyxia. It is also probable that degenerated heart muscle is more subject to these injuries. Ordinarily, however, the vasomotor paralysis dominates the circulatory phenomena until death, the heart beating after the respiration has stopped, although it may not be able to maintain a circulation.

With *faulty administration* the events are quite different. Excessive concentration of the chloroform vapor, particularly when the anesthesia is incomplete, stops the circulation before the respiration. This is the usual mode of chloroform death (Lancet Commission, 1893). If the heart is exposed, it may be contracting feebly, even after the respiration has stopped, so that literally the respiration stops first; but these feeble beats cannot propel the blood, so that, in fact, the circulation usually fails before the respiration.

The cardiac arrest may be due, in individual cases, to direct or reflex vagus stimulation, to asphyxia, to fibrillation or to direct paralysis of the cardiac muscle; or generally perhaps to a combination of these factors. Reflex circulatory disturbances are most dangerous in incomplete anesthesia where the reflex response is active; and in very deep anesthesia, when the low blood pressure may make even slight reflex changes fatal.

Cardiac Changes.—Early in chloroform anesthesia the heart is somewhat quickened, probably by muscular movements and sensory stimuli; or it may be inhibited by the trigeminal vagus reflex. After anesthesia is established, the rate is slowed progressively with increasing narcosis, to cardiac arrest by direct depression of the cardiac muscle or by circulatory collapse.

Circulatory Reflexes.—Chloroform tends to intensify depressive and to weaken augmentor reflexes. The cardioinhibitory response to the *carotid sinus reflex* is intensified (Hering, 1927); the vasopressor response is weakened (Moissejeff, 1926).

Trigeminal (Kretschmer) Reflex.—With rabbits, inhalation of chloroform (also of ammonia vapor) through the nostrils arrests the heart by reflex stimulation of the vagus, but it generally escapes from the inhibition within one or two minutes. The reflex is strongest if the vapor acts simultaneously on the nose and the larynx. There is little response from the pharynx and still less from the trachea (Traina, 1930). The trigeminal reflex is rarely effective in human subjects. Desoubry and Magne, 1914, confirmed that brusque chloroform inhalation produces complete arrest of heart and respiration in dogs and rabbits. However, if absorption of the chloroform is prevented, the arrest is temporary and is followed by rise of blood pressure from splanchnic constriction. In the usual fatal result, therefore, the toxic action of the absorbed chloroform plays an important part in preventing recovery from the reflex arrest.

Vasomotor Center.—The preliminary stimulation is partly due to a direct action of the chloroform, for it occurs when this is confined to the cerebral circulation (by perfusing this from the vessels of a second, chloroformed animal; Gaskell and Shore, 1893). In part, the rise of pressure is also reflex and asphyxial. The vasomotor center becomes depressed early; *f. i.*, the normal vascular compensation against the head-down position is destroyed (L. Hill, 1897). It does not become completely paralyzed until much later. Pilcher and Sollmann, 1915, confirmed that the vasomotor center is depressed directly during chloroform anesthesia. Indirect stimulation may, however, occur when asphyxia is induced by respiratory depression, or if the center becomes suddenly anemic by rapid fall of blood pressure or cardiac arrest. Under such conditions, the center may be violently stimulated, with or without preceding depression. In an intermediate stage of chloroform anesthesia, stimulation of the vasomotor center lowers blood pressure, since chloroform disturbs the reciprocity of antagonistic nerves so that afferent stimuli produce only inhibitory effects; chloroform causes the inverse effects to strychnine. The chloroform vasodilatation may therefore be due to the reversal of the normal pressor impulses of the center. Asphyxia, however, still causes vasoconstriction (Bayliss, 1908). When the vasomotor paralysis is complete, asphyxia does not raise the pressure.

Direct Action on Vessels.—Perfusion of excised organs with chloroform solutions produces a constriction in some organs, dilatation in others, especially the kidneys (Schaefer and Scharlieb, 1904; Filehne and Biberfeld, 1906). The required concentration, however (0.1 per cent), is almost twice as great as that which kills the heart and paralyzes respiration (0.06 per cent), so that this peripheral action can play no part in chloroform anesthesia (Sherrington and Sowton, 1904).

The pressure in the *pulmonary artery* falls, through the cardiac and respiratory depression (Wiggers, 1911).

Cardiac irregularities, ranging from isolated extrasystoles to sudden ventricular fibrillation, may occur at any stage, but especially early in the administration, tending to disappear when the anesthesia is either deepened or lightened. They disappear promptly when the patient wakens (review, W. J. Meek, 1941). *Multiple extrasystoles* are observed in the electrocardiograms of nearly half the patients under chloroform. They are analogous to those which in the *cat* are precursors of ventricular fibrillation under light chloroform anesthesia, which can be prevented or abolished by section of the cardiac sympathetic nerves, and provoked by the stimulation of these nerves or by injections of epinephrine (G. R. Brown *et al.*, 1930). *Dogs* react somewhat differently. Rapid induction frequently produces cardiac arrhythmia and ventricular arrest, but rarely ventricular tachycardia or fibrillation, as in cats. Prompt artificial respiration usually secures recovery, and then the arrhythmia does not return unless there is severe hypoxemia (O. S. Orth and Liebenow, 1946).

Early Stoppage of Heart.—Most fatalities with chloroform occur during the induction of the anesthesia, by sudden arrest of the heart. Experimentally, the heart will often resume if the vagi are promptly divided. In these cases the arrest is due to *stimulation of the vagus center.* This may be *reflex*, due to nasal, laryngeal, tracheal or pulmonary irritation by the chloroform vapor (Dastre; Morat; Brodie and Russell); but it may also occur when all reflex paths are eliminated, or on intravenous injection (Embley, 1902), thus indicating *direct stimulation* of the center. Its excitability is exaggerated by high concentrations of chloroform (about 2 per cent), by morphine and by asphyxia. Deep anesthesia dulls this vagus hyperexcitability, thus explaining why these accidents generally occur at the start. The administration of atropine would prevent this form of fatality. There is, however, another factor; for a normal heart cannot be stopped permanently by vagus stimulation, direct or reflex; with a chloroformed heart permanent arrest is easily produced (Desoubry and Magne, 1914). It follows, therefore, that the high concentration of chloroform vapor must have injured the heart. This increased sensitiveness of the heart may be fatal apart from the vagus: A. G. Levy, 1911, finds the cat's heart in early chloroform anesthesia very sensitive to high blood pressure (epinephrine), death in this case not being avoidable by vagotomy or atropine. This condition disappears in deeper anesthesia and was not seen with ether.

Socin, 1914, showed that chloroform renders the excised heart less resistant to venous engorgement or increased arterial resistance; *i. e.*, that it dilates more easily. Similarly, excitement may stop the heart of lightly chloralized cats (Sollmann, 1908). Embley, 1915, found that early chloroform death with cats is frequently due to ventricular fibrillation. With dogs, this was never witnessed, except as a terminal result of low blood pressure. Hering, 1916, also found the tendency to early death, in dogs and cats, parallel to excitement. The arrest is generally due to ventricular fibrillation from excessive excitability of the heart. Henderson, 1914, was inclined to attribute the early fatalities mainly to acapnia.

Vagus Response.—Chloroform decreases the intensity and duration of cardiac inhibition by vagus stimulation (E. Nobel, 1919).

The *cause of ventricular fibrillation* is presumably a shortened refractory period of the cardiac muscle, described by Sasaki, 1921. Higher concentrations of chloroform paralyze the muscle directly.

Direct cardiac depression by chloroform was demonstrated on the excised frog's heart by Clemens, 1850; on the exposed mammalian heart by Snow, 1852. The *excised mammalian heart* (Langendorff method; Sherrington and Sowton, 1903) shows strikingly the difference between chloroform and ether. The *quantitative difference* in the cardiac depressant action of these narcotics is illustrated by the results of Dieballa, 1894, on perfused frog's heart: if the fatal dose of chloroform be taken as 1, that of ethyl bromide would be 12; of ether, 48; of alcohol, 192. In perfused hearts, and doubtless also in living animals, the depressant action of chloroform is greatly increased by CO_2, and therefore by asphyxia (Sherrington and Sowton, 1906). With frogs' hearts, the depressant effects of anesthetics can be *antagonized by calcium* (Burridge, 1912).

Actions on the blood are not important in ordinary anesthesia. Ether and chloroform, like all fat solvents, produce *hemolysis* when added to shed blood; an insignificant degree of this action seems to occur during life, so that the resistance of the corpuscles is definitely lowered (C. D. Leake *et al.*, 1927). Some polycythemia may occur, especially under ether, due to diminution of the plasma, and to contraction of the spleen in ether anesthesia (amytal relaxes the spleen and so withdraws considerable corpuscles from the circulation; Haussner, Essex and Mann, 1938). The hemoglobin is reduced. Some corpuscles are destroyed entirely, others lose only part of their hemoglobin. Since a diminution of hemoglobin to 50 per cent is dangerous, it is never safe to use anesthetics on patients showing only 60 per cent of hemoglobin (Da Costa and Kalteyer, 1901). It is conceivable that this hemolysis explains partly the *anemia and icterus* which are sometimes seen; but these may be caused by hepatic changes. No methemoglobin is found in the blood after two hours of chloroform or three and a half hours of ether anesthesia (F. Jung, 1943). The *surface tension of the plasma* is lowered by the ether dissolved in it (Trabucchi, 1928). The *specific gravity* of the blood is somewhat increased during anesthesia and for several days after (Sherrington and Copeman). Buck, 1914, described marked decrease of the globulins after about two hours of chloroform or ether anesthesia. The *viscosity* of the blood is slightly increased in deep, diminished in light, anesthesia, but not to an important degree (Burton-Opitz, 1911). The *osmotic pressure* is a trifle increased by the molecular concentration of the dissolved anesthetic (Carlson and Luckhardt, 1908).

The *mineral constituents* of the plasma undergo considerable shift; during one hour of ether anesthesia in dogs, the K was reported to be decreased by 15 to 46 per cent, the Mg was also decreased considerably, Ca slightly, Na and Cl varied slightly and irregularly, with tendency to increase of Cl (Marenzi and Gerschmann, 1933). The *fat content* of the blood is increased by ether; chloroform has this effect only when the animal has been on a fat-rich diet (Bloor, 1914). The *cholesterol content* of the blood increases significantly in ether anesthesia, less so under chloroform, and practically not with ethylene or nitrous oxide. The rise is due partly to the excitement of the induction stage (Hospers, 1933), but it is also proportional to the rise of blood sugar and to the duration of the anesthesia, and may be prevented by the previous administration of insulin. Mahler, 1926, therefore attributed the rise of cholesterol to decrease of insulin output. During surgical ether anesthesia, a *leukocytosis* sets in slowly, usually after one to four hours. It concerns mainly the polymorphous, but the other forms are also increased. It appears to be due to stimulation of the bone marrow. The *phagocytic activity* is not decreased, even after four to six hours of anesthesia (F. C. Mann, 1916). *In vitro*, the motility of leukocytes is somewhat decreased by the concentration of chloroform which occurs in the blood in clinical anesthesia (Lowenburg, 1934).

The *coagulation time of the blood* is shortened in *ether anesthesia* by as much as 40 per cent (Rabinovich). *Chloroform and chloral* have no effect if the coagulation time is normal, but lengthen it if it is abnormally short. *Profound chloroform narcosis* diminishes or abolishes the coagulability of the blood owing to deficiency of plasma fibrinogen and prothrombin. This change is noticeable after thirty-five minutes of anesthesia. In extreme cases the fibrinogen may be completely absent. This effect is connected with the injury to the liver, similar to that of phosphorus, and is not produced by ether. The coagulability recovers with the repair of the hepatic lesions (M. Doyon, 1913; Whipple, 1915; E. W. Schultz *et al.*, 1925; H. P. Smith, Warner and Brinkhous, 1937).

The **pupils** furnish valuable information about the efficiency of the reflexes and asphyxia, and therefore of the depth and course of the anesthesia. In the *excitement stage*, they are dilated with the light reaction moderately decreased. This dilatation cedes with the approach of *anesthesia*. In man there is then actual constriction; the light reaction is diminished or abolished; the eyes are turned inward and upward as in sleep. The constriction persists throughout the anesthetic stage and into recovery. With ether, the diameter averages 3½ to 4½ mm.; with chloroform, 2 to 3 mm. Their behavior is easily modified by reflexes, respiratory embarrassment, and so forth, and should be occasionally ascertained by intentionally changing the depth of anesthesia. *Constricted pupils* usually mean that the anesthesia is light. *Dilatation* may mean either deep anesthesia, or asphyxia, or reflexes with light anesthesia. If the corneal reflex is present, dilatation should lead to more rapid administration; in the absence of reflexes, to lighter administration. *Sudden and extreme dilatation* generally signifies dangerous asphyxia. Morphine and atropine interfere with these reactions.

The effect of anesthesia is identical with that of sleep and is due to the abolition of the cerebral impulses which normally inhibit the constrictor tone of the oculomotor center. Asphyxia, on the other hand, increases this inhibition (Braunstein, 1894). The *pupillary reactions of animals* are somewhat different: all show the dilatation in the excitement and asphyxial stages, and the abolition of the light reflex during anesthesia; but the anesthetic miosis is witnessed only occasionally in dogs, never in cats or rabbits. In these animals the pupils assume a median position. The frog's pupil is not affected by anesthesia (Nakazawa, 1910). The *corneal and conjunctiva-reflexes* disappear late, as in all modes of death. *Nystagmus* under anesthesia occurs from the rhombencephalic supranuclear centers (E. A. Spiegel and Collins, 1940).

Gastro-Intestinal Tract.—Inhalation of the anesthetics generally results in *nausea* and often in *vomiting*, sometimes during the induction, and especially when the patient awakens. The mechanism is mainly central, but the local irritation and the swallowing of mucus may contribute. The degree of postanesthetic nausea depends on the depth and duration of the anesthesia. Ether is perhaps more nauseant than others, and this is exaggerated by its persistent taste, which acts by suggestion. Operative procedures, such as handling of the intestines, may also play a part.

During the surgical anesthesia, ether and, to a still greater extent, chloroform, by their peripheral action on the muscle and on the peripheral innervation, relax the tonus and arrest the movements of the entire digestive tract from the stomach to the rectum. The stomach relaxes, so that the division between fundus and pylorus largely disappears. Acute gastric dilatation is an occasional serious complication. Asphyxia does not overcome the depression. When the administration is discontinued, and if the anesthesia was not too profound or too prolonged, the small intestines and colon recover promptly, and may pass into a period of stimulation, increased colon tonus being especially notable. The stomach recovers more slowly; after deep narcosis, especially with chloroform, complete paresis of the stomach and intestines may persist for two hours, and incomplete paresis for twenty hours. The paresis that commonly follows laparotomies, however, is only partly attributable to the anesthetic, and mainly to the operative procedures (Cannon, 1911). *Other lipolytic narcotics* produce similar depression, but it is relatively slight with barbiturates, and practically absent with ethylene. With *nitrous oxide*, the asphyxial stimulation predominates. During the administration, peristalsis is increased and irregular. After the discontinuance of the administration, marked inhibition follows, but this largely passes off within an hour.

The above observations were made with the fluoroscope (Cannon, 1911; Baron and Barsony, 1914; Kuehlewein, 1921), and on permanent fistulas of the stomach, small intestines and colon (G. H. Miller, 1926). Bhatia and Burn, 1933, found the inhibitory effect of ether on the intestines and uterus much less in fully pithed cats, and therefore concluded that the inhibition is partly supraspinal.

Relative Effect of Different Anesthetic Agents.—Light surgical anesthesia of dogs prolonged the *gastric emptying time* by an average of 64 per cent with chloroform; 40 per cent with ether; 15 per cent with nitrous oxide; about 7 per cent with ethylene, cyclopropane and divinyl oxide. In young normal men, amytal, 0.2 Gm., shortened the emptying time by an average of 20 per cent. The effect on intestinal propulsion is probably similar (E. J. Van Liere, 1943). The *colon tonus and mobility* of dogs are decreased in anesthesia by chloroform, diethylether, divinyl ether; but cyclopropane, ethyl bromide, ethyl chloride and nitrous oxide produce immediate spastic contraction. Barbital has little effect (Van Liere *et al.*, 1944).

The *oral administration of ether and especially chloroform* causes considerable gastric irritation. In milder degree this produces a carminative and anodyne effect, which is useful in colic and dyspepsia (Spirit of Ether, 5 cc., 1 ʒ; Spirit of Chloroform, 2 cc., ½ ʒ; Chloroform Water, 15 cc., 4 ʒ). Spirit of Ether is also employed as a reflex "*diffusible stimulant.*"

If ether is taken into the stomach, it is rapidly volatilized and large quantities distend the viscus, sometimes so much as to interfere with respiration; it may even produce rupture of the organ. The duodenal injection of 2 cc. of ether, through the Einhorn catheter, has been used clinically for *reflex stimulation of pancreatic secretion* (G. Katsch and v. Friedrich, 1922). The spleen contracts actively in ether anesthesia. This is inhibited by nicotine. Barbiturates relax the spleen (Bhatia and Burn, 1933; Essex *et al.*, 1936; Haussner, Essex and Mann, 1938).

Anesthetics on the Parturient Contractions of the Human Uterus.—*Ether and chloroform* inhalations depress, in proportion to the depth of the anesthesia. The effects set in and pass off rapidly. Analgetic doses relieve the pain without materially weakening uterine contractions. Surgical anesthesia abolishes the contractions completely. Colonic ether-oil analgesia, with or without quinine, causes but little depression. *Avertin analgesia,* and *barbiturates* in amnesia dosage, have little or no effect on the contractions. *Nitrous oxide with deep oxygen* does not weaken the contractions even with deep surgical anesthesia. To the contrary, it has a spastic tendency.

Spinal anesthesia with procaine has little if any effect. Stovaine has a spastic tendency. *Morphine* has little if any effect. *Scopolamine* and *atropine* also have little effect, but tend to stimulate. *Quinine* usually has no effect, but it may stimulate or relax. *Epinephrine* tends to produce brief relaxation (Bourne and Burn, 1930; Dodek, 1932; Barlow and Jones, 1934). Similar results have been reported for parturient rabbits (H. Franken and Schossmann, 1928).

Ureter.—The contractions are depressed by chloroform in living animals, even by doses which do not affect the respiration or circulation (Lucas, 1906 and 1907). Inhalation of chloroform therefore relieves the ureteral spasm of *renal colic.* Ether stimulates the contractions.

Urinary Bladder.—Anesthetics (ether, pentobarbital) depress the stretch response and prevent sustained contraction when the bladder is completely filled, so that residual urine remains after micturition (in cats; Kolb and Langworthy, 1938). However, the paresis which may last for some days after abdominal operations is probably due to reflex disturbances, and not to direct effects of the anesthetic.

Skeletal muscle is depressed by the lipolytic narcotics, so that the excitation threshold rises, at first slowly, then rapidly when narcotic concentrations are reached, up to a hundred times the original value. Response to stimulation is slight, slow and localized, but persists until muscle is irreparably injured. Analogous effects are produced by exposure to acetylene, ethylene and nitrous oxide, but these require much higher concentrations (forty, sixty and eighty times, respectively, higher than ether). Nitrogen has little effect even at 10 atmospheres pressure (H. T. Graham, 1929). Potassium contracture is increased by chloroform in anesthetic and higher concentrations; less so by ether (C. Torda, 1944). Chloroform causes a specific *rigor* of the muscle when applied directly or injected into an artery (Kussmaul, 1858; Cl. Bernard). It also coagulates the extracted muscle proteins (Fuerth, 1896). Immersion in saline saturated with ether also results in irreversible rigor. Deep ether anesthesia produces moderate *depression of the motor endings* (Auer and Meltzer, 1914). Chloroform does not have this effect (Githens and Meltzer, 1914). Deep etherization of rats lowers the gastrocnemius muscle potential by an eighth; half of this is due to anoxia. Ether with intocostrin gives about a third greater depression of neuromuscular transmission than the sum of their separate actions (W. Schallek, 1946).

Peripheral Action on Nerves.—The direct excitability of nerves is not materially altered when the central nervous system is completely anesthetized (J. Bernstein, 1870). Direct application of solutions or vapors of the volatile anesthetics to a nerve lowers its conductivity and excitability, changes the polarization (Waller, 1896; Alcock, 1906; Bethe, 1908), and abolishes the action current (Forbes, McIntosh and Sefton, 1916). The sensory fibers succumb before the motor (Longet). The *conductivity of the nerve* is lowered, as well as its excitability; for if a nerve is exposed to ether vapor, stimulation at the proximal end ceases to be effectual much sooner than at the distal end; and with a long stretch of partly narcotized nerve, the response is the smaller, the farther from the muscle the stimulations are applied (Dendrinos, 1902). The excitability is recovered if the ether is washed off in time. With chloroform, recovery is more difficult. The concentrations required for these peripheral effects are greater than can exist in living animals; the motor and sensory nerves remain excitable even in profound anesthesia; nor is the conductivity lowered during life (Forbes, McIntosh and Sefton, 1916). Narcosis of a nerve diminishes its CO_2 production materially. Lower concentrations increase the CO_2 (Tashiro and Adams, 1914). The undiluted anesthetics when *injected directly into a nerve* produce a circumscribed neuritis, enjoining caution in subcutaneous or intramuscular injections.

Special Senses.—The *odor and sweet taste* of chloroform and ether show a peripheral stimulation of these sense organs.

The **urine output** is decreased during anesthesia and for some time after, but is generally compensated so that the twenty-four-hour output is about normal, both as to volume and solutes (Walton, 1933). The decrease is due to increased water loss by sweating, with diminished income because of the nausea; but there appears to be also a more direct action, for most anesthetics prevent diuresis from ingestion of fluid (Heller and Smirk, 1932).

Urine flow may be arrested reflexly by blowing anesthetic vapor (or amyl nitrite) upward through a tracheal cannula so that it passes into the larynx, but not into the lungs, and very little is absorbed.

Ether on Urine Flow.—This is *diminished* during the anesthesia. The oliguria is partly due to increase of blood concentration which is a constant phenomenon of ether anesthesia. Consequently, the decrease of urine can be prevented by increasing the water supply (Barbour and Bourne, 1924). Contraction of the renal vessels, with diminished kidney volume, occurs only in overdosage, and then as a part of the general circulatory disturbance (Buxton and Levy). In surgical patients, the urine output is often diminished by restriction of the water intake (Epstein *et al.*, 1916). As soon as the anesthesia is terminated, the flow *increases*, the output being above normal for several days. The specific gravity is also increased. This diuresis is proportional to the duration of the anesthesia (W. H. Thompson; Hawk, 1911, dogs; Pringle *et al.*, human, 1905).

Chloroform on Urine Flow.—This diminishes steadily during clinical anesthesia (Bobee, 1909), owing to the low blood pressure with diminished kidney volume (Thomson and Kemp, 1898). The *chloride excretion* is increased during and after the anesthesia.

Phenolphthalein Output.—The "functional capacity" of the kidney, as measured by this test, is generally somewhat decreased by ether anesthesia, the more the longer the anesthesia. The output is lowest soon after the operation, returning to normal in twenty-four to forty-eight hours. Exceptionally, there may be no decrease, but rather an increase; or the decrease may be large. It has no relation to albuminuria (R. H. Miller and Cabot, 1915; Epstein *et al.*, 1916). Whipple and Sped, 1915, found the phthalein output lowered after ether, paraldehyde, chloral, chloroform or alcohol anesthesia. They observed that Eck's fistula produced lowered output, as does phosphorus, and therefore attributed the effect to disturbance of liver functions.

Renal Irritation.—Postanesthetic *albuminuria* occurs in about one-fourth of ether anesthesias, and about one-third of chloroform (Wunderlich). Tube casts are common. With previously sound kidneys, the renal irritation usually disappears in a short time. In patients with chronic nephritis there may be fatal suppression of urine; but patients with some albuminuria are often etherized without bad effects. Chloroform is apparently somewhat more injurious than ether, but the difference is not very marked.

Relation of Renal Injury to Age and to the Lipoid Material of the Kidneys.—The renal epithelium of old animals shows greater histologic and functional injury after chloroform or ether, even though the kidney function appeared normal before the anesthesia. This is paralleled by increase of the stainable lipid of the epithelium, which is normally more abundant in old animals, and is further increased by anesthesia, especially in the old. Chloroform is distinctly more deleterious than ether (MacNider, 1921). Foulerton, 1921, attributed the lipid to infiltration from lipemia, owing to hepatic injury.

Anesthetics in Experimental Nephritis.—In dogs rendered polyuric and glycosuric by tubular uranium nephritis, MacNider, 1913, found chloroform anesthesia much more damaging than ether. In full-grown animals, chloroform promptly arrested the urine flow, so that it would not respond to diuretics; it made the histologic lesions more marked. The damage was less in young animals. Ether produced but little effect even in adults. (Young puppies are remarkably tolerant also to the other dangers of chloroform; Whipple, 1912.)

Nitrogen excretion is diminished during ether anesthesia (Pringle, 1905); it is then increased for twenty-eight to forty-eight hours, depending but slightly on the duration of the anesthesia. The total increase may amount to 45 per cent, but is generally smaller, and therefore much less than with chloroform (Hawk, 1908). Chloroform anesthesia *increases* the total nitrogen excretion (especially in carniverous animals), and the ammonia, allantoin, diamino acids, polypeptids, creatinine and organic sulfur. It *decreases* the excretion of urea and of monoamino acids (Lindsay, 1911). The increase persists for some days and may amount to 300 per cent. These changes are similar to those of phosphorus poisoning, and probably depend on the hepatic lesions.

Gaseous Metabolism and Blood Gases.—The production of CO_2 is decreased during anesthesia, by a third or a half; but the disturbances of respiration interfere with the gas exchange (Henderson), and thus raise the CO_2 concentration of the blood and lower the oxygen saturation.

The *CO_2 content of the blood* is increased from 25 to 36 per cent, the oxygen content reduced from 13.6 to 8.1 per cent (Gardner and Buckmaster, 1910). Chloroform depresses the gas metabolism of the *brain* by 60 to 90 per cent, proportional to the depth of the narcosis. With ether, the CO_2 falls less than the oxygen; the reverse is true of morphine (Alexander and Cerna, 1913). In *nerve fibers*, direct exposure to low (stimulant) concentrations increases CO_2 production, while anesthetic concentrations depress it (Tashiro and Adams, 1914). In *plants*, anesthetics first increase and then depress gaseous metabolism (Osterhout, 1918).

The *temperature* falls during anesthesia by ether and chloroform, partly through diminished heat production, partly through increased heat loss. The diminished production (Scheinesson) is reflected in decreased CO_2 formation, and is due to the decreased muscular movements and tone. The increased loss of heat is due to narcosis of temperature regulation, aided by exposure, and a little by the cooling action of the vapor. In ether narcosis (as after section of the spinal cord), cold reflexes fail to produce the normal protective blood concentration (Barbour and Bourne, 1924). In the paralytic stage, the dissipation of heat is also diminished by failure of the circulation, but the diminished heat production predominates in the collapse. The body becomes practically poikilothermal, and if the coma is of long duration, the temperature may reach a low level, unless heat is applied artificially.

Clinically, chloroform and ether cause about an equal fall of temperature. In ordinary operations on man the fall is from 1° to 4° F., averaging about 2.5° F. (H. A. Hare, 1888); much more in prolonged operations on animals (Moore, 1919). It is not markedly increased by the ordinary dosage of morphine. It can be prevented by external heat (the room temperature should be above 26.5° C. = 80° F.) and by keeping the skin dry (S. G. Davis, 1909). Excessive heat must be avoided, since temperature regulation is disturbed in all directions. Etherized dogs can maintain a constant body temperature only if the environing temperature is near 31° C. (Barbour and Bourne, 1924). *Precautions against loss of heat* are especially important, since chilling favors the occurrence of postanesthetic pneumonia. Warming the vapor has been advocated (Gwathmey, 1908), but the loss of heat from this source would be insignificant (Boothby, 1913).

Anesthetic hyperglycemia and glycosuria may occur temporarily in ordinary ether anesthesia (animals, Hawk, 1904; after intravenous injection, King, Maple and Haupt, 1913; human, Roehricht, 1905), and especially with chloroform (E. L. Scott, 1914). They are less with barbiturates (C. L. Evans *et al.*, 1931). Amytal and chloralose are said to cause the least disturbance of carbohydrate metabolism (Best, 1935). Ether completely inhibits the hypoglycemic action of insulin in dogs; the hypoglycemia sets in when the ether wears off (S. A. Peoples, 1943). The hyperglycemia involves extensive mobilization of liver glycogen (King *et al.*, 1912) which may fall by 60 per cent in the course of an hour's ether anesthesia (Evans *et al.*, 1931). Several factors are involved: asphyxia, through liberation of epinephrine and by acidosis; cooling; and perhaps direct stimulation of a diabetic center (Campbell and Morgan, 1933). The utilization of the mobilized dextrose may be normal or impeded (C. L. G. Pratt, 1938). The reducing action of the urine is partly due to ascorbic acid, especially in dogs, whose ascorbic acid synthesis is increased up to fifteen times the normal (Bowman, 1937); other reducing substances are perhaps present after chloroform (Hawk, 1911).

Ether hyperglycemia is more intensive in well-fed dogs than after fasting (Hawk, 1911). Chloroform diminishes the tolerance to galactose and levulose (Marshall and Rowntree, 1915). The *diastatic activity* of the blood increases in ether anesthesia, parallel to the rise of blood sugar (Killian, 1917). Ether and nitrous oxide increase the glycosuria and D ÷ N ratio in *phlorhizin diabetes*, the extra sugar being derived from glycogen, probably through tissue asphyxia (Sansum and Woodyatt, 1915).

Anesthetic hyperglycemia occurs after *division of the splanchnics* (King, etc., 1911), but only to a slight degree (Keeton and Ross, 1919). *Atropine* reduces the hyperglycemia considerably (Ross, 1919). It is checked by *barbiturates,* although these do not inhibit epinephrine or pituitary hyperglycemia (Campbell and Morgan, 1933). *Epinephrine output* is not indispensable to ether hyperglycemia, for this can readily be induced after excision of the adrenals (G. N. Stewart and Rogoff, 1920); but the *epinephrine store* is decreased by etherization; not by trauma (Stewart and Rogoff, 1920). Chloroform, ether and chloral decreased the output of epinephrine from perfused out suprarenal glands (Antischkow, 1927). Hawk, 1911, attributed the ether glycosuria to dyspnea. Grube, 1911, believed that the cooling is a factor, and this was confirmed by Tachi *et al.*, 1926. Ross and McGuigan, 1915, claimed a direct action of the ether, and that asphyxia and excitement are not essential.

Acidosis.—Inhalation anesthesia, whether by ether, chloroform or nitrous oxide, tends to produce some acidosis, with fall in *p*H and in the reserve alkali (bicarbonate) in the blood, and with the occurrence of acetone in the blood; but there is no evidence that it is of sufficient degree to be significant in clinical surgery (Menten and Crile, 1915; Austin and Cullen). The decrease of reserve alkali is greatest with chloroform (Morris, 1917).

With clinical ether anesthesia, compensated acidosis occurs in 30 to 85 per cent of routine operations; uncompensated acidosis in 15 to 20 per cent. The average reduction in plasma bicarbonate is equivalent to 5–15 cc. of CO_2 per 100 cc. The acetone substances of the blood are increased, accounting for at least 60 per cent of the bicarbonate decrease, and perhaps for all (Reimann, 1919). Killian, 1917, claimed that the *oral administration of sodium bicarbonate,* 20 Gm. per day, corrects not only the diminished alkali reserve, but also the hyperglycemia. It would be especially indicated if the CO_2 capacity of the plasma before operation is less than 58 cc. (Reimann and Bloom, 1918). The fall is not due to hyperpnea, for it occurs also under uniform artificial respiration. It is prevented by inhaling air with 3½ per cent of CO_2; 3 per cent is ineffective. MacNider, 1921, found the alkali depletion much more marked with old than with young animals; it was also greater with disturbed kidney function. W. E. Stone, 1938, found the *lactic acid content of the brain* decreased with barbiturate or ether anesthesia. Acetonuria is frequent after ether or chloroform anesthesia (Marshall and Rowntree, 1916; ethyl chloride, Telford, 1906; even after local cocaine, Gundrum). With ether, it is not much influenced by the duration of the anesthesia; fasting may be a factor (Chalfant, 1912). It is more common with the closed than with the open methods of administration. Children are more susceptible. J. J. Short, 1920, however, found the acetone substances in the blood and urine practically unchanged in patients who had been under ether for three-quarters of an hour; with more prolonged administration there was a slight increase.

Leake *et al.*, 1923, concluded that the *mechanism of the acidosis* is by withdrawal of base, and not by acid production, and that hyperventilation plays a very small part. Seevers, Stormont *et al.*, 1939, found that hyperventilation during clinical anesthesia produces marked alkalosis, with an average rise of 0.25 *p*H and lowering of CO_2 tension of arterial blood by 21 mm.

Alkali Reserve on Potency of Anesthetizs.—Tiffeneau *et al.*, 1930, reported that anesthetic potency is increased by administration of acid and decreased by alkali.

Delayed Chloroform Poisoning (Postanesthetic Toxemia).—The prolonged administration of chloroform may be followed by fatty degeneration of the liver, heart, kidneys, leading to profound toxemia, vomiting, prostration, icterus, and coma which is often fatal. Chloroform administration should, therefore, not be continued longer than half an hour. Postanesthetic toxemia is especially common with children and old people, in pregnancy, and in patients with acetonuria, diabetes, hepatic disorders (Hildebrandt, 1913), cyclic vomiting, rickets or wasting diseases. Anesthetics that do not contain chlorine and bromine are much less liable to toxic hepatitis. Avertin with amylene hydrate causes more liver damage than ether. Nitrous oxide, ethylene, evipan and cyclopropane are apparently free from this effect (unless there is anoxia), as are also local and spinal anesthesia (S. M. Rosenthal and Bourne, 1928; L. M. Morrison, 1943). Similar hepatic changes are produced by elementary phosphorus, by compounds of arsenic and of selenium, by tars, and by some bacterial infections. Abundant diet rich in carbohydrates (Graham, 1917; MacNider, 1929) and casein furnishes considerable protection against chloroform (and arsenical) hepatitis, while fat, and fasting, increase the susceptibility (W. C. Davis and Whipple, 1919, standardized dogs; L. L. Miller and Whipple, 1942; Ravdin *et al.*, 1943).

Symptoms.—The importance of late chloroform poisoning seems to have been first recognized by Bevan and Favill, 1905, although cases had been reported previously. The symptoms start after ten to 150, generally twenty-four to forty-eight hours, the intervening time being indistinguishable from the normal course. They consist in profuse, sometimes incessant, vomiting, first bilious, then blood-stained; excitement and delirium, alternating with apathy and prostration; dilated pupils; rapid pulse; icterus; unconsciousness deepening into coma. Death occurs in four to five days (Herb, 1911). *Necropsy* shows degenerative lesions in many organs, chiefly in the liver, brain, medulla, kidneys, suprarenals and heart; minor changes in the pancreas and gastro-intestinal tract; none in the ovaries, testes, lymph glands, spleen and thyroid (Risi, 1939; halogenated hydrocarbons, rats and mice, Abreu *et al.*, 1944). The *blood* generally shows retention of nonprotein nitrogen, urea and amino acids, similar to phosphorus poisoning, though less intensive (E. K. Marshall and Rowntree, 1915). All the current *liver function tests* reveal impairment by chloroform, carbon tetrachloride and other halogenated anesthetics (Drill and Ivy, 1943, bromsulfalein and serum phosphatase; L. M. Morrison, 1943, bile salt concentration in urine; Rosenthal and White, 1938, bromsulfalein and icteric index). Eight days are required for return to normal if the chloroform anesthesia lasted half an hour, and six weeks if it lasted two hours. The *anatomic lesions in the liver* consist in extensive vacuolization, fatty degeneration, swelling and necrosis of the cells, especially about the central veins (Nothnagel, 1866; Whipple and Sperry, 1909; Herb, 1911). Hypodermic injection of chloroform in paraffin oil leads to hepatic lesions similar to those of human Laënnec cirrhosis (Iwata and Inui, 1940). The fatty changes are perhaps due to infiltration and not to degeneration (Foulerton, 1921. Large doses of other anesthetics [urethane, Sollmann] cause similar degeneration). The icterus, the disappearance of fibrinogen from the blood; the diminution of liver lipase, with increase of plasma, kidney and muscle lipase (Quinan, 1915); the delay of the biliary excretion of phenoltetrachlorphthalein (Whipple and pupils, 1913); the changes in metabolism; and the occasional occurrence of leucin and tyrosin, are analogous to acute yellow atrophy and to phosphorus poisoning. In animals which recover, the liver changes tend to return to normal, even when there has been extensive necrosis (Whipple and Sperry, 1909). Mosiman and Whipple, 1912, found that puppies and fetuses are less subject to the hepatic necrosis; and that pigeons, frogs and terrapin seem to be immune. The *impairment of bile excretion* by chloroform, carbon tetrachloride and phosphorus is parallel to the histological changes of the parenchymal cells, and not of the stellate cells, suggesting that the latter are not concerned in bile pigment excretion (Wakabayashi, 1928). (The bromsulfalein retention test appears the most suitable indicator of hepatic dysfunction in animals; J. Casals and Olitsky, 1946.)

Protection against chloroform hepatitis is furnished in dogs by preliminary injection of casein digest, methionine, or sodium thioglycolate, not by sodium thiosulfate or glutamate, dextrose or gelatin. The common factor in the protection appears to be the -SH group (Brunschwig *et al.*, 1945). *Methionine* gives material protection if administered within three hours before the chloroform. It would probably also be of some value for treatment (3 to 5 Gm. daily; J. H. Eddy, 1945). It is chiefly responsible for the protective effect of casein and large amounts of meat. Cystine is also protective, but other amino acids are not (L. L. Miller *et al.*, 1940; Miller and Whipple, 1942). Protection is also furnished by hypodermic injection of *irritants*, such as sodium *xanthine* (Forbes and Neale), sodium ricinoleate or colloidal carbon. It has been suggested that the subcutaneous inflammation makes protein cleavage products available to the liver (Vars *et al.*, 1939). Administration of *liver extract* is somewhat protective in rabbits, chiefly but not entirely through its xanthine (J. C. Forbes, 1939). Davis and Whipple, 1915, obtained no protection from alkalis. Epinephrine and quinine appeared somewhat protective, the epinephrine, however, only after a day. The addition of other liver poisons did not markedly modify the effects of the chloroform.

Histologic lesions occur also in other organs, especially fatty and degenerative changes in the epithelium of the straight and convoluted tubules of the kidneys (Howland and Richards; Apperly, 1812); in the pancreas (Whipple and Sperry); in the suprarenal cortex and other glands of internal secretion (Scaglione, 1915). Involvement of the heart muscle sometimes dominates the symptoms. Degeneration of the cardiac ganglia has been described (Strassmann, 1898). Small hemorrhagic foci exist in the gastro-intestinal tract, mesentery, pleura and pericardium (Herb). These histologic lesions can be produced, especially in young dogs, by chloroform anesthesia lasting two hours (Whipple and Sperry, 1909; Whipple and Hurwitz, 1911). Repeated chloroform anesthesia, with rabbits, produces degenerative changes also in the central nerve cells and those of Auerbach and Meissner plexuses. So do many other poisons, but not ether (Lissauer, 1914). Cragin and Hull, 1911, pointed out the similarity of the late chloroform phenomena to *eclampsia*, and suggest that chloroform would be much more injurious than ether in this condition. McCrudden, 1912, reported that chloroform is more likely to produce fatty changes of the rabbit's heart after *nephrectomy*. Ether does not do this. *Encephalopathy* occurs occasionally after prolonged anesthesias. Necropsies show a great variety of degenerative lesions of the cortex and basal ganglia, probably due to anoxia (Steegmann, 1939).

Experimental hepatic cirrhosis occurs after repeated administrations of chloroform (Mertens, 1896; Herter and Williams, 1905). It is favored by the presence of bacterial infections and may then proceed to acute yellow atrophy (Opie, 1910).

Intravenous injection of ether (large doses in rabbits) causes destruction of liver tissue, with extensive thrombus formation (prevented by leech extract). The mechanism is evidently altogether different from ordinary chloroform degeneration (L. Loeb, 1906; Loeb and Meyers, 1910).

Other after-effects of anesthetics are mainly due to the irritant action, and may therefore occur with either anesthetic. They may be recapitulated as: *Gastric irritation, nausea and vomiting* are almost universal; less so with open methods; they vary with duration of anesthesia. *Tympanites* occurs especially after abdominal operations; the anesthetics are only contributory. *Renal irritation* is about equally frequent with either anesthetic. *Aspiration pneumonia* is more frequent after ether.

Protoplasmic Toxicity and Local Irritation.—The anesthetics, on direct application, narcotize all cells, of the lower organisms as well as of the higher. This is preceded, at least in some cases, by evidences of stimulation. The concentration required for irritation is greater than is reached from systemic administration. At the place of application, however, the irritation is marked. Chloroform is more irritant than ether, with equal concentration, and can be used as a rubefacient or even vesicant.

Cutaneous Irritation.—The evaporation of the volatile anesthetics cools the skin. Local anesthesia by freezing may thus be produced (see "Ethyl Chloride"). With ether and especially chloroform, the cooling is succeeded by a burning sensation and rubefaction. If evaporation is prevented, this may proceed to vesication. Chloroform is therefore used as an active counterirritant (chloroform 30, soap liniment 70). Local application of chloroform or of carbon tetrachloride relieves the itching of *insect bites* (W. A. Hoffman, 1941). The irritant action on mucous membranes is even more violent.

Hypodermic injection of ether is employed (1 to 2 cc.) as a rapid reflex stimulant in collapse, but it may lead to ulceration. It tends to produce slight and transient rise of blood pressure; but it fails in the severer grades of hemorrhage and shock, and in anesthesia (Lieb and Herrick, 1917). The *respiration* of normal rabbits is stimulated by the hypodermic injection of chloroform or ether; but these have little effects on deeply morphinized animals (Hanzlik, 1923).

Antiseptic Action.—Ether is quite ineffective for sterilizing the *skin* (G. T. L. Archer, 1945), but good results are claimed for ether in the *disinfection of wounds*, rinsing superficial wounds with liquid ether, or pouring 5 to 20 cc. into deeper wounds, repeating several times (Koristensky, 1930). In *perforating peritonitis*, 50 to 75 cc. are poured into the peritoneum (30 cc. for children). It is claimed that this diminishes the mortality without increasing the incidence of adhesions or pulmonary complications, or other untoward effects (Souligoux, 1913; Ducreux, 1938). *Chloroform* is fairly antiseptic (Strassmann, 1888; Salkowski, 1891). Chloroform water is used as a preservative.

Vermifuge.—Chloroform has been employed for the expulsion of tapeworms, but the effective doses are too irritant and toxic to make its use advisable. Alessandrini, 1915, advised it against hookworm and other parasites, 3 to 4 Gm. in olive oil or castor oil. Darling *et al.*, 1918, did not find it very effective. The **narcotic effects on infusoria** were observed by C. Bernard, 1876. The *action on fishes* is described by Clayberg, 1917, and utilized for bio-assays.

In plants the narcotics abolish protoplasmic movements; cause plasmolysis; suppress the gross movements of the Sensitive Plant (Mimosa pudica). Exposure to chloroform and especially to ether vapor hastens blooming (Keeble, 1906). The assimilation of oxygen is abolished by fairly low concentrations of chloroform; whereas CO_2 production is stimulated even by considerably higher concentrations Excessive concentrations, however, paralyze this also (A. A. Irving, 1911). Dry seeds resist high concentrations of anesthetics, because the dry envelopes of the seeds are impermeable. If these are removed or punctured, anesthetics become injurious (B. Schmid, 1901).

Ferments.—Pepsin, rennin, trypsin, diastase, invertase, catalase and other organic ferments, as well as metallic catalysts, are restrained by anesthetics in the same general order of efficiency as living cells.

CHOICE OF THE ANESTHETIC

This is determined by the particular conditions of the patient and of the operation. Safety should be the first consideration, but the depth and duration of anesthesia, the comfort of the patient, and the convenience of the operator are also important. The principal anesthetics which deserve consideration are: general anesthesia by ether, chloroform, nitrous oxide, ethylene, cyclopropane, vinyl ether or avertin; with or without morphine, scopolamine and barbiturates; seconal or pentothal; spinal anesthesia; and local anesthesia.

For *short operations*, local anesthesia by procaine or similar drugs should be preferred. Where these are not practicable, nitrous oxide or cyclopropane are used. Nitrous oxide is the safer. It is practically devoid of danger in short anesthesia. For *longer operations*, the advantages of general anesthesia often outweigh the disadvantages, as compared with spinal anesthesia. *Chloroform* is far more dangerous than ether, ethylene or nitrous oxide, although with practical experience the acute dangers may be greatly reduced. The chief immediate risks are in the induction period. The danger of postanesthetic toxemia makes its employment in prolonged operations almost inexcusable. *Cyclopropane* is more toxic to the heart. It has perhaps a special value in *shock*, as it tends *to raise blood pressure*. Nitrous oxide with oxygen and ether has variable effects on blood pressure, but is probably safer. Pentothal and spinal anesthesia lower blood pressure and so present a special risk (Crooke *et al.*, 1944).

Ether, ethylene and nitrous oxide are practically equally safe in ordinary cases. *Ether has several advantages:* it is easily administered; it gives more complete relaxation, less asphyxia, and less rise of blood pressure; so that the condition of the respiration and circulation are more nearly normal. Its administration is simple and does not require so much experience; ether is perhaps the safest anesthetic for long operations. The disagreeable features of its induction can be practically avoided by skillful administration. The advantages of nitrous oxide and ethylene appear especially in the cases in which ether is specifically contraindicated.

Contraindications to Ether.—The irritant action contraindicates its use (and also that of chloroform) in *renal disease* and in *acute respiratory disease* (colds, bronchitis). In these, nitrous oxide is preferred, although ether is often employed without damage. Chronic respiratory disease is not a contraindication, unless there is actual dyspnea (emphysema). *Children* are especially subject to ether irritation, resulting in respiratory embarrassment and choking. Ether *favors bleeding*, especially in parts in contact with the vapor; it is therefore not popular for operations of the mouth and larynx. In *brain tumor or atheroma*, ether and especially nitrous oxide may produce apoplexy; avertin, or local or spinal anesthesia, should be preferred. *Advanced heart disease* makes all anesthetics more dangerous. In this respect, ether and nitrous oxide are about equal; both should be preferred to chloroform and cyclopropane. The danger is proportional to the functional condition rather than to the valvular lesion; with fair compensation, ether can be used safely; indeed, the circulation may be rather improved during the anesthesia. In advanced fatty degeneration, it is better to employ local or spinal anesthesia. In *hot climates*, above 93° F., ether is vaporized so rapidly that its use by the ordinary methods is difficult.

Nitrous oxide is perhaps the safest anesthetic for short operations, and in sequence with ether. If the anesthesia lasts longer than an hour, it becomes somewhat more dangerous than ether even in the hands of experts; it is much more dangerous with limited experience. It is more pleasant to take; it causes no irritation, and but little excitement or gastric disturbance. There are practically no after-effects. It is especially preferred for short operations, and for excitable and neurotic patients. Old individuals are good subjects. Its *disadvantages* are, that the muscular relaxation is less complete; it causes more or less asphyxia and abnormal rise of blood pressure; and it requires special apparatus and special experience for its successful administration. Obese or anemic patients are also unsuited to all anesthetic methods which interfere with respiration.

Ethylene is in most respects intermediate between ether and nitrous oxide. It is discussed in a separate section.

Chloroform is convenient for patient and operator: its action is much more rapid than that of ether; it induces the most profound anesthesia and relaxation; it does not have the disagreeable taste, causes less suffocation, less excitement, and less postoperative nausea and vomiting. These disagreeable features of ether can be largely avoided by proper administration (preliminary nitrous oxide, and open-drop method). The dangers of chloroform may be risked in emergencies; when prompt anesthesia is imperative; in brain surgery, atheroma and aneurysm, where the lowered blood pressure is advantageous; and possibly on the battlefield to increase speed and lessen bulk. Chloroform has no advantage over ether in renal disease, and but little in respiratory diseases. *Specific contraindications to chloroform* are: advanced heart disease, Graves' disease, hemorrhage, prolonged operations, and conditions which favor acidosis.

Chloroform in Obstetrics.—It was generally believed that the use of chloroform in childbirth is relatively safe (J. Hill, 1916). This is explained partly by the lesser apprehension of the patients, and partly by the light degree of anesthesia, or rather analgesia, which ordinarily suffices. For deep anesthesia, it is as dangerous as for other patients, and presents the added disadvantage of delaying labor and thus favoring postpartum hemorrhage. The analgetic dosage does not cause serious delay. The anesthetics pass into the fetal circulation (Jung, 1914), and prolonged anesthesia is probably as injurious to the child as to the mother.

Statistics of Anesthetic Mortality.—Reliable statistics of sufficient extent will not be available until the reporting of *all* anesthesias, good and bad, is compulsory. Even then, the ratio of "bad risks" will be indefinite. Existing statistics give only a rough idea of the relative danger, but they agree fairly well. According to the various compilations, the acute mortality for *chloroform* is given as 1:1000, 1:2075, 2500, 3000, 3500, 3700, 5900; a fair estimate would seem to be 1:3500. This does not take account of the delayed deaths. For *ether*, the figures run 1:5100, 14,000, 14,600, 16,500, 16,800, 23,200; the average would be perhaps 1:16,000. For *A.C.E. mixture*, the ratio is 1:3370; for *ethyl bromide*, 1:5400; for *ethyl chloride*, 1:3000, 7000; for *nitrous oxide* in short operations (dentistry), less than 1:5,000,000. Beecher, 1938, gives 1:500 to 1:2000 for avertin, 1:2000 for chloroform, 1:3500 for cyclopropane, 1:5000 for ether, and 1:50,000 for nitrous oxide.

ADMINISTRATION OF GENERAL ANESTHETICS

Preparation of Patient.—A cleansing enema may be given on the evening preceding the operation, and an interval of five hours should have elapsed since the last meal, which should not be too heavy. The patient should be examined for cardiac, renal and pulmonary disease. He should be placed in such a position as to interfere to the smallest possible extent with respiration, the head preferably low and turned to the side. The clothing should be loosened and all foreign bodies—false teeth, and so forth, removed from the mouth. To prevent the local action of ether or chloroform on the skin, the mouth and nose may be anointed with petrolatum. Care should be taken to have the patient close the eyes.

Administration.—Inhalation is superior to all other methods in the convenience of its application, and in the facility with which the depth of anesthesia can be regulated to suit the needs of the moment. This depends on the concentration of the anesthetic vapor and can be adjusted either by using exactly dosed mixtures of anesthetic and air or, more simply and on the whole more efficiently, by watching closely the condition of the patient. The response of the respiration, pupils and other reflexes to changes in the concentration of the vapor must be observed. The concentration can be increased either by pouring the anesthetic more rapidly, by applying the mask closer to the face, or by limiting the supply of air. The mask should at first be kept fairly away from the mouth, until some narcotic effect is obtained, to lessen the feeling of choking from the concentrated vapor. The patient should be encouraged to breathe quietly and regularly. Counting is a good expedient for this purpose. If the patient holds his breath, struggles or coughs during the induction of the anesthesia, the concentration should be temporarily reduced, not increased. Rapid and deep breathing lessens the concentration of the anesthetic by dilution and cooling, when inhaled from gauze. Slow and shallow breathing gives more concentrated vapor.

Management during Recovery from Anesthesia.—The patient should not be left until he is fully conscious, since vomiting and inspiration of mucus may cause asphyxia. No nourishment should be given for at least four hours. If vomiting is persistent, a tumbler of hot water with a teaspoonful of bicarbonate may be given. Recovery is usually more speedy and satisfactory if the patient is placed on his side.

Regulation of Anesthesia.—Mechanical devices do not replace the sense of responsibility, the constant watchfulness and the quick reasoning of the experienced anesthetist. Anesthetization is not a physical experiment where the factors can all be foreseen; the condition of the patient may vary from moment to moment, and must be taken into account. The state of the respiration must be carefully watched: if the patient holds his breath, the mask must be held farther away, since the next respiration will be an especially deep one. When the respiration becomes slow and shallow, a sufficient amount has been taken, and the concentration may then be diminished. The aim is to give no more than is necessary just to keep the patient anesthetized. On the other hand, care must be taken to keep him thoroughly under the influence, for excitement, struggling, stoppage of respiration, shock and overdosage are much more common under partial or uneven anesthesia. Since the respiration and circulation react one upon the other, so that no change could occur in the latter without being noticed in the former, and since most accidents occur from stoppage of the respiration, it may be sufficient to watch this alone, as is advised by some. But as it is of the highest importance to discover beginning failure of the one or the other at the earliest possible moment, both should be carefully observed. *Severe hemorrhage*, exceeding 20 cc. per Kg., materially lowers the necessary dosage of the anesthetic (D. R. Wood and Jaco, 1943).

Closed and Open Methods of Administration.—The anesthetics may be administered with or without free access of air. In the closed methods, the patient rebreathes more or less from a permanent mixture of vapor through a fairly air-tight mask or cone. In the open methods, he breathes air freely through gauze (the usual chloroform mask), on which the anesthetic is poured. The closed methods are more rapid and economize the anesthetic, but from other standpoints they are rather objectionable. The open methods avoid asphyxia and are therefore pleasanter, safer and less subject to after-effects (mucorrhea, vomiting, and so on). The apparatus is simpler and more easily sterilized. Henderson, 1915, advised a closed method with ether vapor, claiming that this is scarcely more unpleasant than nitrous oxide and produces less nausea, vomiting, gas pains, and the like, than other methods. The skin should be kept pink, neither pale (acapnia) nor dusky (asphyxia).

Carbon Dioxide Inhalation.—In the induction of anesthesia, the stimulation of respiration by 5 per cent carbon dioxide hastens the attainment of equilibrium between the anesthetic vapor and the tissues, and therefore permits the use of lower concentrations. This should diminish local irritation (Haggard, 1924), and permits the use of more oxygen in gas anesthesia; for instance, the induction of anesthesia in rats or cats required 90 per cent of ethylene, leaving only a 10 per cent margin for oxygen; but it could also be attained with a mixture of ethylene, 75; oxygen, 15; and carbon dioxide, 10 (Kleindorfer, 1931). The carbon dioxide should not be unduly prolonged. Y. Henderson and Haggard, 1918, advised *postanesthetic inhalation* of air containing 1 to 8 per cent tension of carbon dioxide. This stimulates the respiration, and so promotes the more rapid elimination of the ether.

Administration of Ether by the "Cone" Method.—A special mask is used, which admits only a limited amount of air. About a tablespoonful is poured in the mask, and repeated as needed. The fact that the required concentration of ether is much greater than with chloroform leads to the temptation not to admit sufficient air. Concentrations of ether above 7 per cent irritate the mucosa so strongly that in imperfect anesthesia they cause reflex coughing, closure of the glottis and suffocation (Dreser, 1893).

Ether by the "drop" ("open" or "perhalation" method) avoids to a great extent the irritation, suffocation and excitement of ordinary ether anesthesia. This more than compensates for the disadvantages, the relative slowness, waste of ether, saturation of the room, and refrigeration of the inspired air. In this method, the ether is dropped rapidly (about 150 drops per minute) over the entire surface of an open (chloroform) inhaler, covered with some eight layers of gauze, and held an inch from the face. If the mask is closely applied, the vapor concentration may rise to 9.3 to 10.8 per cent; never above 12 per cent. (The method was originated by L. H. Prince, 1895.)

Administration of Chloroform.—This is dropped on a few layers of gauze, supported by a frame, and held some little distance from the face. The rate should never exceed 60 per minute, and usually should not be over 12. After the anesthetic stage has been induced, 6 drops per minute will usually suffice.

The *quantity of anesthetic* required for an ordinary operation varies. Some 40 cc. of chloroform or 150 cc. of ether by the ordinary method, or 250 cc. by the drop method, may suffice for an hour's anesthesia.

Other Methods of Administration.—Anesthetics may be administered by other methods, but these demand special experience, and generally special apparatus. In operations about the face, the anesthetic may be inhaled through a *nasal catheter;* in operations on the thorax, it may be administered by tracheal insufflation.

Intratracheal Insufflation.—The insufflation of air passed over the anesthetic was elaborated experimentally by Githens and Meltzer, 1913. It eliminates respiratory paralysis as a fatal factor. *Ether* is especially safe: excessive doses first stop the spontaneous respiration, but this is immaterial since the insufflation constitutes an efficient artificial respiration. The blood pressure declines slowly, and recovery is possible during an hour after the respiration is arrested, by simply stopping the ether. With *chloroform,* the respiration and circulation fail together, so that there is no reliable danger sign, and the zone of safety is much narrower. Unskillful insufflation presents various dangers (George, 1917). In *intrapharyngeal insufflation* ether vapor is driven through a nasal catheter, usually after anesthesia has been induced by the open method.

Rectal insufflation of the warmed ether vapor is useful in operations about the head; it also avoids excitement, struggling and gastric disturbance. It acts promptly (within six to fifteen minutes) and can be maintained indefinitely. However, it is uncomfortable; the dosage is more difficult; it is liable to be followed by severe, sometimes fatal, irritation of the colon, with gas distention, colicky pains and bloody diarrhea (Cunningham, 1920). The fatality is fairly high. Operative anesthesia may be produced by the rectal injection of a mixture of equal parts of *ether and oil.* Several fatalities have occurred, presumably because the dosage has not been satisfactorily worked out. *Gastric administration* of an alcoholic solution of chloroform is used in animal experimentation, but is too dangerous for man.

Intravenous administration of saline solutions of the anesthetics (ether, 5 per cent, Burckhardt, 1910; 7.5 per cent, Rood, 1911; chloroform, 0.6 per cent, Giani, 1910) produces anesthesia; but *a priori* one would consider the method both unsatisfactory and dangerous; and this seems to agree with the practical experience (Tyrode, 1910). The *solubility of ether in normal saline solution* falls with rise of temperature. A hundred cc. dissolve 11.2 Gm. at 5°; 6.9 at 20°; 5.3 at 30° (Bennett, 1912). The *intramuscular injection* of undiluted ether has been tried. However, the method is uncertain, painful and dangerous (see J.A.M.A., 1912, *59:*288).

Induction of anesthesia during sleep is of some medicolegal importance. It is difficult, but cases are reported (Brouardel, Les Asphyxies, p. 199). False accusations of criminal assault are often based on the mental confusion of the patient in the induction stage.

Administration for Analgesia.—Short operations can be performed in the stage of confusion before the patient becomes unconscious. This is also utilized in *obstetrics*, to deaden the pain without relaxing the uterine contractions; and to *check convulsions*, such as those of strychnine, tetanus or eclampsia. It is especially useful in the onset of these conditions. When the convulsions are fully developed, it must be used cautiously to avoid asphyxia. For the production of this light anesthesia, chloroform is preferred to ether, since it can be more easily regulated, and its effects are more lasting.

"One-minute Ether Anesthesia."—A teaspoonful of ether is poured into the cone, and the patient directed to count and take deep inspirations. The operation is done as soon as the counting becomes irregular.

Fixed Dose Self-Inhalation Chloroform Analgesia.—A single dose of 5 cc. of chloroform, poured on cotton and inhaled from the hand, produces effective analgesia, with slight confusion, but without unconsciousness, nausea or dangerous effects. The action is complete in five minutes and lasts about twenty minutes. The method has been used successfully for painful dressings and short operations (Sollmann, 1918; Sykes, 1919).

Obstetric Self-Inhalation of Chloroform.—Brunton's method may be used when an anesthetist is not available. The inside of a tumbler is covered with blotting paper. A few drops of chloroform are poured on, and this is given to the patient, with directions to hold it an inch from her mouth and inhale. This works automatically, for as the patient becomes narcotized she allows her hand to drop, and so removes the tumbler; and as soon as she becomes conscious and sensitive to pain, she replaces it.

Ether analgesia by oral administration has been employed for similar purposes. The action is more lasting, but not always as efficient. The dose consists of an ounce of a 50 per cent solution of ether in liquid petrolatum, sandwiched between two drinks of port wine. The petrolatum is intended to act as an automatic regulator for the evaporation and absorption of the ether vapor (Gwathmey and Karsner, 1917). A similar suggestion has been made for ethyl chloride (Baskerville and Hirsch, 1921).

Absorption and Excretion.—Chloroform and ether are absorbed almost instantly from the lungs, and excreted rapidly and almost quantitatively by the same channel. A small part is excreted by the urine. Absorption from the stomach and rectum is also prompt, and may be utilized for anesthesia.

Retention.—The percentage of the anesthetic in the expired air is at first much less than in the inspired. It begins to rise after two minutes, but remains considerably below the inspired even after ten minutes (Brodie and Widdows, 1906). This shows an actual retention of the anesthetic, which is reflected by its level in the blood (Buckmaster and Gardner, 1907). The *equilibrium between air, blood and tissues* depends on their relative solution-affinity for the anesthetic. The exchange is rapid at first, but slows as equilibrium is approached. Consequently, although a uniform concentration of anesthetic is inhaled, the concentration of the blood continues to increase for over eight hours; and when the anesthetic is discontinued, the excretion extends over the same period (Nicloux). The equilibrium between blood and tissues is probably established more promptly, for the concentration in the venous and arterial blood soon becomes equal. The anesthesia depends upon the concentration in the brain, and this on the concentration in the blood multiplied by their partition coefficient. The ether solubility in hashed brain is to that in blood as 0.92 to 1.31. The other tissues play the role of a buffer (Haggard).

Final Elimination.—When the anesthetic is discontinued, the greater part disappears rapidly from the blood.

Within five minutes, the percentage of ether or chloroform has fallen to one half. The final elimination is more gradual: with ether, there are traces in two hours, but not in four hours. With chloroform, the concentration falls to only a seventh in three hours, and traces are present even in seven hours (Nicloux). The excretion of volatile anesthetics through the lungs is a merely physical process, analogous to their evaporation from aqueous solutions. It depends more upon their solubility and affinity for water than on their boiling point (Cushny, 1910).

Ultimate Fate.—*Ether* is not oxidized in the body; 79 to 92 per cent can be recovered from the expired air, and practically all the remainder from the other excretions (Haggard, 1924). A small smount of *chloroform* is decomposed in the tissues, with the production of chloride (excreted by the urine; Zeller, 1883) and carbon monoxide. The quantity of the latter is too small to produce any effects. This decomposition occurs also in shed blood (Nicloux, 1910). The decomposition of various *bromine-containing anesthetics* is discussed by G. H. W. Lucas, 1928.

Concentration of Anesthetic in Inspired Air.—The anesthetics exist in the blood and tissues solely in physical solution: they are therefore absorbed and excreted by the alveolar blood in proportion to their concentration in the alveolar air, until the whole system of air-blood-tissues is in equilibrium. The absorption into the blood and tissues is not instantaneous, so that a given concentration in the blood can be reached the more rapidly, the more concentrated the anesthetic vapor, and the more effective the respiration (Haggard, 1924). With fairly uniform administration, the exchange is sufficiently rapid so that the quantity of anesthetic in the tissues at any given moment depends essentially on the concentration (partial pressure) of the anesthetic vapor in the inspired air (P. Bert). The action is determined by this concentration, or rather by the partial pressure, and only in a minor degree by the absolute dose of the anesthetic. The gas concentration in air may be expressed as volumes per cent, as mm. of pressure, or as mg. per liter. These may be converted into each other on the basis that 1 per cent by volume = 7.3 mg. Hg pressure at about 20° C., at sea level = 3.08 mg. of ether or 4.97 mg. of chloroform per 100 cc. of air.

The effective concentrations agree closely for all mammals, including man, provided that time is given to establish equilibrium (Bert, 1884; Dreser, 1893). In clinical practice, however, this is rarely the case. The administration is generally started with a high concentration to hasten induction, and this is gradually reduced as anesthesia is reached; the clinical concentrations are therefore variable, but almost always higher than at equilibrium. With *ether*, the maintenance concentration under clinical conditions is about 6 per cent by volume (18.5 mg. per 100 cc. of air, 44 mm. tension) for light surgical anesthesia; 10.5 per cent by volume (31 mg. per 100 cc. air, 73 mm.) for complete abolition of reflexes; and 11 per cent by volume for stoppage of respiration and eventual death (Kochmann, 1914). In surgical operations on man, T. K. Kruse, 1924, found the ether concentration under the mask to average 7 per cent after ten minutes of anesthesia. Boothby, 1916, found the "anesthetic tension" (the partial pressure of ether vapor which maintains anesthesia indefinitely, after it has been established) as 47 mm., equivalent to about 6.7 volumes per cent. In routine hospital practice, the alveolar air concentration of ether ranges from 3 to 7.2 volumes, according to the type of operation (R. N. Harger *et al.*, 1941). Experimentally, with induction sufficiently slow to secure equilibrium with the blood and tissues, satisfactory ether anesthesia is attained with 4 to 4.5 per cent by volume; and respiratory failure with 6.7 to 8 per cent.

For *chloroform*, the corresponding concentrations are, for light anesthesia, 1.35 volumes per cent (6.8 mg. in 100 cc. of air); deep narcosis, 1.65 per cent; fatal, 2 per cent (Kochmann, 1914). The *anesthetic zone* between the minimal anesthetic and the fatal dose is much wider for ether (*viz.*, 5 per cent) than for chloroform (0.65 per cent). This is one reason for the greater safety of ether. Another difference is that the deep anesthesia can be maintained almost indefinitely with ether, while chloroform kills within one or two hours (Rosenfeld, 1896). The *time factor* therefore plays a part especially with chloroform (also on account of the postanesthetic degenerations). On the other hand, the concentration may rise momentarily above the fatal limit, since the absorption, although rapid, is not instantaneous. Under clinical conditions 1 per cent chloroform vapor is insufficient to induce anesthesia; 2 per cent is generally effective; less than this must be used in pathologic conditions, but requires a longer time to establish narcosis. Even 3 per cent may be necessary in exceptional cases. The maximum limit of safety is placed at 2 per cent by Waller; at 1 to 1.5 per cent by Embley. Therefore, as soon as anesthesia is reached, the concentration must be gradually reduced to 1 per cent, and after half an hour even lower.

Even perfectly adjusted mixtures are not absolutely safe. In practice the inconveniences of exact vapor mixtures are generally held to outweigh their advantages. However, the above figures are fairly approximated in the ordinary methods of administration. *The air under the ordinary mask* has been found to contain generally from 1 to 2 per cent of chloroform, and with rapid application, up to 4 per cent.

The **distribution of the anesthetics in the blood and tissues** is in accordance with their relative solubility and vapor tension, if time suffices to establish equilibrium. *In vitro*, at body temperature, the stable distribution of ether between air and blood approximates 1:14.9 (Haggard, 1924). Ether is somewhat more soluble in water, making its quotient 1:15. In life this equilibrium is not reached even in the alveoli, and the quotient is nearer 1:10 (B. H. Robbins, 1934 and 1935). As long as the tissues continue to take up anesthetic from the blood, and this continues even to the end of three hours of anesthesia (van Mechelen, 1926), the concentration is higher in the arterial than in the venous blood, and this is higher than in the tissues. The left heart is therefore exposed to a higher concentration than the right, especially if the anesthetic is "pushed" (Pohl, 1891). When the administration is discontinued, the sequence is reversed, so that the concentration is highest in the tissues and lowest in the arterial blood.

The *distribution in the tissues* is influenced by their content of lipid material (Frison and Nicloux, 1907) especially of cholesterol and lecithin, for anesthetics with high lipid affinity such as chloroform. The proteins are also concerned. *With ether*, which has a relatively smaller affinity for lipids, the percentages in the plasma, corpuscles and in all the tissues are practically equal when equilibrium is reached (Nicloux); but the greater blood supply of the brain causes it to take up the anesthetic more rapidly, so that its concentration is temporarily higher than that of other tissues.

Ether Concentration in Venous Blood.—The following figures are representative for jugular blood of dogs (Robbins, 1935): light anesthesia without loss of reflexes, 113 mg. of ether per 100 cc. of blood; full anesthesia with suppression of lid and corneal reflexes, 150 mg; arrest of respiration, 187 mg.

The dangerous *concentrations of ether* in the blood were determined for cats by Schram, van Leeuwen and Made, 1916: 0.13 to 0.14 per cent, corresponding to deep anesthesia, cause marked fall of blood pressure by action of the vasomotor center and vagi; 0.17 per cent is fatal unless artificial respiration is used. With artificial respiration, 0.25 per cent is fatal if the vagi are active; 0.31 per cent if they were paralyzed; 0.44 per cent is fatal to the isolated heart-lung preparation, and 0.5 per cent to the perfused heart. The perfused heart is but little damaged by 0.17 per cent, *i. e.*, the concentration fatal to intact cats. During good anesthesia, the ether concentration in the *gases of the peritoneal cavity* reaches about 4 per cent (Y. Henderson, 1918). The *concentration of ether in the urine* approaches that in the arterial blood (Haggard, 1924). A *micromethod for the isolation of ether* is described by Gettler and Siegel, 1934.

With chloroform, blood absorbs considerably more than does salt solution; the percentage is two and one-half to eight times greater in the red corpuscles than in the plasma (Pohl, 1891; Nicloux, 1906; Buckmaster and Gardner, 1907). *Ethylene* also gives decidedly higher concentration in the plasma. The hemoglobin appears to be concerned in this, as well as the lipids (Nicloux). Data on the solubility of chloroform in blood, serum and water are given by Nicloux, Scolli and Foglieni, 1928.

The *concentration of chloroform in blood and tissues* was investigated especially by Nicloux, 1906 to 1908; Mansion and Tissot, 1906; Sicard, 1906. According to these, the *arterial blood* contains, with complete anesthesia by chloroform, 0.032 to 0.05 per cent (0.014 to 0.028 according to Buckmaster and Gardner). At death, the chloroform concentration averages 0.08 per cent (0.06 per cent, Pohl; 0.04 per cent, Buckmaster and Gardner). The *cerebrospinal fluid* also contains small quantities of chloroform when this is inhaled (Hald, 1921). The *chloroform content of the brain* is relatively high; that of the *liver*, low. In dogs killed by chloroform, Gettler and Blume, 1931, found 0.037 to 0.048 per cent of chloroform in the fresh brain; 0.035 to 0.048 in the lungs; and 0.019 to 0.028 per cent in the liver. Nicloux obtained similar figures. The white substance contains more than the gray, and peripheral motor nerves more than sensory, agreeing with their lipoid myelin content (McCollum, 1930). However, Guenter and Hoelscher, 1906, claimed that there is no difference in the percentage of chloroform in the blood, brain, liver and kidney, provided that the inhalation of a given concentration is kept uniform until equilibrium becomes established. *Adipose tissue* contains no more than does muscle (Nicloux), the walls of the fat cells being difficultly permeable to lipoid solvents. The distribution of chloroform in *hen eggs* exposed to the vapor was studied by Lallemand, 1932.

MIXED ANESTHETICS

Mixed Anesthesias.—Attempts to blend the actions of volatile anesthetics by mixing them are unsuccessful, because the ingredients do not volatilize with equal rapidity (Snow). The composition of the inspired anesthetic is therefore uncertain. As a rule, during the administration, the concentration of chloroform increases. The administration is further complicated by the different sequence of the disappearance of the reflexes with chloroform and ether (Storm van Leeuwen, 1916). These mixtures are therefore at least as dangerous as chloroform, and should be condemned (Kochmann, 1903).

The principal mixtures of this type are the *English A.C.E. mixture*, introduced by Harley (A_1; C_2; E_3);[*] *Billroth mixture* (A_1; C_3; E_1) *C. E. mixture of Hewitt* (C_2; E_3); *Schleich mixture* (benzine 1; C_3; E_{10}). Other mixtures containing ethyl chloride or bromide, and so forth, have also found advocates. The alcohol and benzine of these mixtures were intended mainly to raise or lower the boiling point, but benzine is not indifferent. There seems to be some combination between ether and chloroform, for on mixing equal volumes (25 cc.), the temperature is said to rise 14° C. (Marcelet, 1912).

Synergism of Ether and Chloroform.—Analysis of the concentration of the anesthetics in the blood shows that mixtures of the vapors do not exhibit a potentiated effect, but a rather imperfect summation of action (Madelung, 1910, and Buergi, 1910). Damkoehler, 1913, obtained different results for different depths of anesthesia.

Sequence Anesthesia.—A material advantage may sometimes be gained by using a sequence of anesthetic agents, particularly to induce anesthesia by the pleasant and promptly acting nitrous oxide-oxygen inhalation, and to continue with ether. These may be preceded by a sedative dose of morphine and a full hypnotic dose of a barbiturate, to produce a basic narcosis. This probably presents the nearest approach to an ideal anesthesia. Changing from full ether anesthesia to chloroform is dangerous (Hewitt).

Morphine, Scopolamine or Atropine Preliminary to Anesthesia.—One or several of these drugs may be injected hypodermically, half an hour before starting the operation. They diminish the anxiety of the patient and avoid some of the dangers of anesthesia. The doses given below may be combined.

Morphine (10 to 15 mg., $\frac{1}{6}$ to $\frac{1}{4}$ grain) is most effective in decreasing apprehension, excitement and struggling. Labbé and Guyon, 1872, were the first to use it clinically. It makes anesthesia prompter and smoother. It reduces materially the quantity of anesthetics (Claude Bernard), and thereby the gastric, pulmonary and toxic after-effects. The patient does not awaken so early. Since the morphine narcosis involves an entirely different mechanism, the side effects of both are relatively smaller. On the other hand, morphine depresses the excitability of the respiratory center, and the miosis interferes with the pupil danger signal. Morphine is contraindicated in pulmonary disease, in semicomatose patients, or when the operation would involve bleeding into the air passages.

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[*] The proportions of all the mixtures are by volume. *A* stands for alcohol; *C*, for chloroform; *E*, for ether.

Morphine reduces the concentration of ether or chloroform vapor required for light anesthesia, but not that for deep anesthesia or death. The margin of safety is therefore widened considerably—60 per cent for chloroform, 50 per cent for ether (Kochmann, 1914). However, the respiration must be carefully watched with chloroform, for this also shows dangerous potentiation (W. Straub, 1913).

Atropine (0.3 mg., 1/200 grain) also diminishes ether salivation and bronchorrhea, thereby lessening the occurrence of ether pneumonia. The atropine mydriasis and tachycardia interfere with the use of the pupil and pulse as danger signals. The above dose should not be exceeded on account of occasional idiosyncrasies.

Scopolamine (0.5 mg., 1/120 grain) is often substituted for the atropine. It has the same peripheral actions on the pupil and glands, but intensifies the narcotic effects of morphine. On the other hand, it disposes to pronounced vasodilatation, so that the pressure may fall as deeply in ether anesthesia as with chloroform (Mayor, 1908). It sometimes intensifies the respiratory depression of morphine to a dangerous degree. Bevan, 1915, who opposed it strongly, believed that it also increases the percentage of vomiting and of bladder paresis.

The combined action of morphine or scopolamine with the hydrocarbon narcotics is far more than simple addition (Knell, 1907). Madelung, 1910, and Rappaport, 1911, found that one-half to two-thirds of the ordinary concentration of anesthetics suffices. *Scopolamine alone* does not reduce the concentration of chloroform or ether required for light anesthesia, but lessens somewhat that for deep anesthesia. Scopolamine and morphine together resemble morphine, except that they do not increase the zone of safety. The anesthesia is deeper, however; this may be practically important (Jochmann, 1914). *Bromides* give practically only simple summation with morphine or the aliphatic narcotics (Klammer, 1913).

Basal anesthesia is the extension of the preanesthetic sedation to the degree of confusion, sleep or stupor, as a foundation which is then brought to full anesthesia by an inhalation anesthetic agent. It is induced by fixed doses of rather potent, rather briefly acting narcotics, barbiturates or avertin, and is discussed more fully under these drugs. It is a sequence anesthesia, the sedative acting as a "back-log" of partial narcosis which avoids the fright and other difficulties of the induction period, and assures a smoother course, with much smaller quantities of the anesthetic; and on the other hand it obviates the inflexibility of fixed anesthetics. The respiratory depression, however, is additive and may be distinctly greater than with inhalation alone.

Ether-Magnesium Anesthesia.—The combined use of these anesthetics was proposed by Meltzer, 1913, for laboratory animals. Le Heux, 1919, showed that there is only simple summation between magnesium salts and ether, chloral and urethane. Gwathmey *et al.*, 1924, introduced a more complex *combination for obstetric analgesia.* They administer 0.01 Gm. of morphine hypodermically; one to three hypodermic injections of 2 cc. of 50 per cent magnesium sulfate; and a colon injection of ether 75 cc., quinine hydrobromide 0.6 Gm., and olive oil, to make 120 cc. It has been shown, however, that the magnesuim is quite inactive in this dosage (Shackell and Blumenthal, 1932), and the quinine does not serve any useful purpose. The inefficient magnesium has now been displaced by oral administration of pentobarbital (Gwathmey and McCormick, 1935).

The causes of death under anesthesia must be understood in order that accidents may be avoided. They differ according to the anesthetic, the stage of anesthesia, the character of the operations, diseases of the patient and other conditions. On this account clinical accidents may be different from the usual laboratory experiments.

Death Not Always Due to Anesthetic.—Patients died on the operating table before anesthetics were invented. One such case was of considerable importance in the history of anesthesia. When Simpson was about to try chloroform on a patient for the first time, the orderly who was carrying the bottle fell and spilled the chloroform. No other being obtainable, Simpson proceeded to the operation without anesthesia. The patient died with the first cut. Had the chloroform been given in this case, its introduction into practice might have suffered a long delay. Other similar cases are not unknown: a patient was to be operated upon and demanded chloroform. His condition, however, was so low that the surgeon feared to grant his wish, and to calm him held a cloth *without* chloroform before his face. Scarcely had the patient made four inhalations—of air—when he was dead. Many other cases of sudden death from the violent mental impression could be cited, besides deaths undoubtedly due to traumatic shock (Strassmann, 1898).

Impurities which may occur in ether and chloroform, mainly by decomposition, are rather unimportant. They contribute to the local irritation, but probably not to the dangerous effects. Anesthetic fatalities seem to be as frequent with the "pure" chloroform or ether as with that not specially treated. However, only U.S.P. quality should be used clinically. In the event of accident, inquiry should be made whether other patients have reacted abnormally to the same lot of anesthetic.

Ether, when kept in contact with air without special precautions, undergoes auto-oxidation, hastened by heat, light, moisture and other factors. This results in acetaldehyde, acetic acid, and an unidentified *"ether peroxide,"* which is explosive when ether is evaporated, and which is probably responsible for most of the aberrant pharmacological actions (G. Lindgren, 1946), although the irritant aldehyde is probably also involved. These chemical changes may be avoided or retarded by careful preservation, or by the addition of 0.02 per cent of diphenylamine, which is harmless in this concentration (Lindgren). Bruns, 1895, concluded from clinical observation that the ether impurities are mainly responsible for the bronchitis (R. B. Smith, 1913). Henderson, 1914, considered poor ether as more excitant, disposing to acapnia. Ether also generally contains some ethylene, which is probably unimportant. The effects of adding impurities to ether are reported by W. Browne, 1926. The presence of alcohol slows the rate of evaporation, and may be necessary when the ether is used in high altitudes or at a high temperature. The *impurities of chloroform* are also due to oxidation, accelerated by light and acids. The products vary with the conditions. The most constant are the irritant phosgene (carbonyl chloride) and hydrochloric acid.

Preservation.—The U.S.P. directs that *ether for anesthesia* must be stored in tight containers of not more than 3 Kg., and must not be used if the container has been opened longer than twenty-four hours. Carefully controlled clinical comparisons showed no difference, however, between ether so stored and that kept in bulk (Hediger and Gold, 1935; Dooley *et al.*, 1935; Morrison, 1938). No deterioration occurred within a month when a large tin container was opened daily and part of the contents removed (Hediger *et al.*, 1940). Lindgren, 1946, found that the peroxide tends to slow the induction time in animals and proposes that the peroxide, expressed as H_2O_2, should not exceed 5 mg. per 100 cc. Sunlight leads to rapid deterioration, and clear glass should not be used; amber glass is better, but tin is best (H. Gold, 1942). Chloroform should be preserved in sealed, dark glass bottles, and should contain 1 per cent of alcohol, which acts as a reducing substance.

"Idiosyncrasy," in the sense of allergy, probably does not exist for general anesthetics; nor are there marked differences in susceptibility toward equivalent concentrations of the anesthetic, even with refractory patients (Boothby, 1914). The greatest practical differences in the reaction of patients consist in the manner of "taking" the anesthetic. They are therefore most conspicuous in the induction of anesthesia, which is peculiarly difficult in alcoholic patients. Boothby, 1913, attributed their resistance to deep breathing, blowing the ether off the mask. Morphinists are said to be relatively insusceptible. Patients with Graves' disease may react badly. A patient may tolerate one anesthetic better than another. After the anesthesia is established, there is but little evidence of "peculiar" reactions, except such as may be foreseen in heart disease. Fatal accidents should therefore not be lightly ascribed to idiosyncrasy. The postanesthetic toxemias, however, are undoubtedly influenced by the individuality of the patient.

Range of Susceptibility.—In a series of *dogs,* the amount of ether required to produce analgesia ranged from 0.4 to 1.1 cc. per Kg. of body weight (median 0.65 cc.); the smallest amount that stopped respiration was 1 to 3.3 cc., median 1.65 cc., per Kg. The margin of safety was five times greater in some than in others (R. W. Whitehead and Draper, 1936), but this refers to the amount inhaled, not to the concentration. *Very young mice* are materially more resistant to arrest of respiration by ether than those somewhat older; in an ether concentration which killed mice older than twenty days in four and one-half minutes, mice less than four days old survived about one hundred minutes (Barrows, 1933). *Starved animals* are much more susceptible to chloral, paraldehyde and morphine, but not to alcohol, amylene hydrate, or urethane (Mansfeld, 1905). *Dextrose administration* previous to ether anesthesia of pregnant animals tends to stabilize their acid base equilibrium, and to guard them against kidney injury. It is more effective in young animals than in old, and in early more than in late gestation (MacNider, 1926). *Alcoholic intoxication* of dogs materially increased the toxicity of prolonged chloroform inhalation, even when the alcohol had been administered three or four hours previously and its visible effects had practically disappeared (S. M. Rosenthal, 1930). *Hyperthyroidism* induced in guinea pigs by feeding thyroid gland rendered them more susceptible to heart block by chloroform, but not by ether (Herzfeld, 1926).

Death during the induction of anesthesia is fairly common with chloroform, rarer with ether. In a series of twenty *chloroform deaths* in which the time was noted, a third occurred within five minutes, and a half between six and fifteen minutes after the start of the administration (quoted from Brouardel, "Les Asphyxies," 1896). The usual sequence of events is sudden suspension of the respiration from acapnia or muscular spasm; the asphyxia leads to cardiac dilatation, vagus stimulation and finally asphyxial failure of the heart. The failure is especially rapid with *chloroform*, because this adds the direct cardiac action of the drug. In light chloroform narcosis, the cardiac muscle is hyperexcitable, and any excitement is likely to induce ventricular fibrillation and death (G. Levy, 1913; G. R. Brown, Long and Beattie, 1930). The respiration may resume temporarily after the heart has stopped, but the heart itself cannot usually be revived. Failure of the circulation therefore commonly precedes the final arrest of respiration and is the real cause of death. Prompt artificial respiration generally restores the heart, and the arrhythmias do not return when chloroform is resumed, unless there is severe hypoxemia (Orth and Liebenow, 1946).

With *ether*, similar fatalities are rarer, but may occur early or somewhat later—in either event owing to faulty administration during incomplete anesthesia. The error may have been committed an hour before actual death: In light ether anesthesia, the excitability of the respiratory center is increased. If this state is prolonged by excessively slow, incomplete or intermittent anesthesia (*f. i.*, in throat operations), acapnia results. When the anesthesia deepens and the center becomes depressed, the acapnia (deficiency of CO_2) leads to arrest of respiration and injury to the heart (Henderson, 1911). Stoppage of respiration by *ether* is less dangerous, because the more vigorous heart generally beats until the respiration has resumed. Experimentally, the heart may also be stopped reflexly by vagus stimulation, but clinically this seems to be exceptional. At any rate, the phenomena occur with little warning. The *danger signs* are sudden dilatation of the pupils, pallor and change of facial expression. Too high concentration of the vapor is the immediate cause of these actions. Fright, excitement, struggling, irregular respiration and idiosyncrasy are contributing factors. Crying in children is especially dangerous. These accidents are avoided by beginning the administration with very dilute vapor, and increasing the concentration gradually. Morphine helps to prevent acapnia and fear. Atropine eliminates the vagus reflex.

Epinephrine-Chloroform Syncope.—Epinephrine is valuable for resuscitation when cardiac arrest occurs in deep narcosis; but in *light* anesthesia, its injection may produce dangerous arrhythmias and fatal ventricular fibrillation, especially with the halogenated narcotics, chloroform (A. G. Levy, 1911 and 1913), methyl and ethyl chloride and bromide, trichloroethylene, carbon tetrachloride, and large doses of avertin. Cyclopropane (see Index) renders the heart subject to epinephrine fibrillations. With chloroform the fibrillation does not occur if the epinephrine is injected *before* the anesthesia, nor in *deep* anesthesia. It is most marked in vagotonic patients, and is much greater in cats than in dogs. It is due chiefly to excessive irritability of the chloroformed heart muscle to adventitious stimuli, such as epinephrine, acceleration, stimulation, abrupt and excessive changes of blood pressure, and sensory reflexes. It may be prevented or suppressed by quinine, quinidine, procaine, cocaine and barbiturates (review, W. J. Meek, 1941).

Death in deep anesthesia is usually due to paralysis of respiration, generally with more or less involvement of the circulation. With *ether*, the circulation is usually fairly good when the respiration stops. The arrest may be due to exaggerated response to inhibitory reflexes, especially from the vagus or superior laryngeal (Mann). With *chloroform*, there is progressive fall of blood pressure, then failure of the respiration, and finally cessation of the heart; but the pulse is generally imperceptible before the respiration stops. Since the paralytic phenomena develop gradually, with ample warning, these deaths are generally due to inexperience of the anesthetist. The *danger signals* are: increasingly shallow or irregular respiration; very slow or very rapid pulse, cyanosis; dilatation of pupil. These accidents may be avoided by carefully watching for these signs, by maintaining the anesthesia evenly, and no deeper than complete muscular relaxation and absence of the sensitive reflexes. The *autopsy* in acute chloroform or ether deaths shows nothing beyond the ordinary phenomena of death by asphyxia—heart distended, veins congested, and so forth.

Late Ether Convulsions.—Dangerous epileptiform convulsions, setting in during deep anesthesia by ether or other anesthetics, have been noted occasionally, especially in England (R. V. Payne, 1936). They are rare, but occur especially in children and young women, particularly in those with febrile conditions. They are quite distinct from nitrous oxide jactitation, and from the "ether clonus" that develops before full anesthesia is obtained. They start with dyspnea and cyanosis, soon followed by generalized convulsions which begin in the eyelids and spread to the facial muscles and over the entire body. The temperature rises very high. Nearly a third of the patients die, usually within one-half to three-quarters of an hour, by arrest of respiration (Lundy, 1937). Many of the patients have abnormal electroencephalogram records, indicating latent epileptic liability which would be a predisposing factor (D. Williams and Sweet, 1944). A. Smith, 1944, reports that the convulsions may be arrested by raising the patient to a sitting position, thus lowering the intracranial pressure. Seevers *et al.*, 1938, attributed the convulsions to depletion of alkali reserve, by respiratory depression, rebreathing and fever, and found that CO_2 potentiates similar ether convulsions in animals. Oxygen variations had little effect. *Experimental catatonia from gases* always results if white mice inhale N or CO_2; inconstantly with CO and N_2O; not with acetylene (de Jong, 1934).

Swallowing of chloroform usually produces immediate vomiting and sometimes defecation, followed by narcosis (Schoenhof, 1914). The acutely *fatal dose* is not known; an ounce or more would be dangerous. Recovery may be succeeded by fatal gastritis or icterus and the other phenomena of late chloroform poisoning. The treatment would be as for inhalation. Gastric lavage with oil has been advised (Wirth, 1909).

Treatment of Accidents.—The *tongue* may fall back and interfere with respiration, as denoted by noisy breathing. If this occurs, "place the index finger of each hand upon the corresponding cornua of the hyoid bone, while the middle fingers rest upon the angle of the jaw, and then press forward and upward, the same force serving to extend the head upon the neck; if this fails to open the glottis, by means of a tenaculum, thrust far back into the base of the tongue, draw it forward" (H. C. Wood). If the mucus accumulates, it should be removed with a cloth (Mayor suggests the dental saliva siphon).

Serious accidents should be treated with the first warning of danger; the anesthetic should be stopped at once. The head of the patient should be lowered to give the medullary centers and heart the full benefit of any remaining circulation. A few rhythmic compressions of the epigastrium may be tried, but if these do not succeed quickly, *artificial respiration* by any of the methods should be begun at once. This prevents asphyxia and eliminates the poison. The cardiac region should also be compressed strongly at the rate of 40 times per minute, since this aids the action of the heart and supplies a mechanical stimulus. A liter of saline solution and 1 cc. of 1:1000 solution of epinephrine may be at the same time injected into the cardiac end of an artery. The chances of success are proportional to the promptness with which they are applied. Gunn and Martin, 1915, recommended the combination of intrapericardial injection of epinephrine with cardiac massage. This may be successful even when the heart is arrested and when either measure alone would fail. Various stimulants are usually tried, at present especially metrazol, but their efficacy is questionable.

Reflex stimulation, by the inhalation of diluted ammonia or by any strong sensory stimuli, is sometimes remarkably effective in early anesthesia, but may depress respiration and blood pressure if the anesthesia is deep. *Metrazol* varies for different anesthetics (in dogs); under ether it produces marked tremors and convulsions, with little or no respiratory stimulation; under evipal it causes marked stimulation of the respiratory center without convulsions; under trichlorethylene it has both effects (D. E. Jackson, 1934). Draper and Whitehead, 1939, found that intravenous injection of 5 mg. per Kg. in late surgical ether anesthesia had a distinct tendency to prevent arrest of respiration. Coramine did not counteract respiratory arrest by either chloroform or ether, nor did it facilitate resuscitation (Whitehead and Draper, 1938). Strychnine, caffeine, digitalis and nitrites are probably useless.

Explosion Hazard.—Most anesthetic vapors are highly inflammable and explosive, especially if mixed with oxygen. Chloroform is not explosive, but forms dangerous irritant oxidation products. Nitrous oxide is not easily explosive and lowers the explosiveness of other gases. Ether ignites and explodes readily; ethylene and cyclopropane are especially liable to explosion. The occasions for anesthetic explosions are open lights, cautery and static electric sparks. Moist air furnishes more efficient protection against these than does grounding. Open ether administration offers little danger of explosion, as air taken 2 inches from the mask is not inflammable (Coste and Chaplin, 1937). However, the flame of an open light may leap over considerable distance, especially if there are drafts. If an open light is unavoidable, it should be placed high above the patient, since ether vapor is heavier than air.

Statistically, the hazard of explosion is small; a questionnaire covering over two million administrations gave the rate, per 100,000 as 1.73 for ether, 2.44 for hylene, 3.85 for cyclopropane (P. D. Woodbridge 1939). The *approximate limits of inflammability of ethylene and ether* are reported by Coward and Jones, 1931, as: ethylene in air, 3 to 30 per cent; in oxygen, 3 to 80 per cent; ether in air, 1.7 to 50 per cent; in oxygen, 1.7 to 40 per cent; in nitrous oxide, 3.8 to 26 per cent. Coste and Chaplin, 1937, state the inflammability limits of ether vapor as 2 to 8 per cent in air, 1.5 to 16 per cent in nitrous oxide and in oxygen.

Chloroform, if used with an open light, is partly oxidized into phosgene gas ($COCl_2$, carbonyl chloride), chlorine and hydrochloric acid, which cause considerable irritation—cough, dyspnea, collapse (Langenbeck, 1888). Fatality to the spectators has been reported (see Gerlinger, 1902).

PREPARATIONS.—***Chloroform,** U.S.P., contains at least 99 per cent $CHCl_3$ and 0.5 to 1 per cent of alcohol. Heavy, colorless, volatile liquid; boils at 60° to 61° C. Characteristic odor, sweet hot taste. Not inflammable, but in presence of flame produces noxious gases. Slightly sol. in water (1:210); freely miscible with alcohol, ether and oils. Dose, 0.06 to 0.3 cc., 1 to 5 minims. *Chloroform Water*, U.S.P., is a saturated aqueous solution. Dose, 15 cc., 4 drachms. *Chloroform Liniment*, U.S.P., is a mixture of 3 volumes of chloroform and 7 volumes of camphor and soap liniment. It deteriorates with age.

***Ether,** U.S.P. (Aether; Sulfuric Ether), contains 96 to 98 per cent ethyl oxide, $(C_2H_5)_2O$. Light, volatile liquid; sp. gr., about 0.715; boils at 35° C. Characteristic odor. Highly inflammable; vapors explosive. Sol. in water (1:12) and in all proportions of alcohol and oils. Dose, 1 cc., 15 minims. *Ethyloxide*, U.S.P., is a less pure product, used as solvent, and not for anesthesia. *Spirit of Ether*, B.P. (Hoffmann's Drops), contains 33 per cent of ether. *Compound Spirit of Ether* (Hoffmann's Anodyne) is an antiquated preparation of about the same strength as the spirit, containing additional ethereal products ("ethereal oil").

NITROUS OXIDE

Nitrous oxide, N_2O, nitrogen monoxide or protoxide, "laughing gas," was the first of the inhalation anesthetics. When inhaled undiluted, it rapidly produces unconsciousness and anesthesia, partly by a direct narcotic action, and partly by exclusion of oxygen. The asphyxia limits its use to short operations, such as the extraction of teeth. It has the advantages of prompt action and recovery, absence of irritation and of after-effects, and is practically devoid of danger. By the addition of oxygen, the asphyxial factor may be removed. The anesthesia also becomes slower and lighter, but by carefully adjusting the percentage of oxygen a satisfactory degree of surgical anesthesia can be maintained for longer periods without letting the asphyxia attain dangerous proportions. Nitrous oxide is especially valuable in the "Gas-Ether Sequence," by avoiding the unpleasant features of the induction of ether anesthesia. Asphyxia by undiluted nitrous oxide is used in the treatment of schizophrenia.

Historical.—Nitrous oxide was first prepared by Priestley about 1776. The discovery of its anesthetic properties by Humphry Davy and by Wells is described under "Ether and Chloroform." Elsworth (Boston Med. and Surg. Jour., 37) in January, 1843, amputated a thigh under successful nitrous oxide anesthesia. Its administration with oxygen was introduced by E. Andrews of Chicago in 1868. *Gas-ether sequence* was suggested by Clover, 1876.

Inhalation of Undiluted N_2O.—For short operations, as in dentistry, the gas is administered through a tight-fitting mask, so that all air is excluded. The symptoms run a rapid course: the *preliminary effects* consist in a sweetish taste; numbness; exhilaration (laughter); confusion; deeper and quicker respiration; and fuller pulse. *Partial anesthesia*, with loss of consciousness, ensues in twenty to thirty seconds. The patient is subject to dreams. The reflexes are preserved and excitement may be present, especially if the patient is disturbed. The respiration is still regular, deep and quickened; the pulse full and rapid; the pupils are enlarged; the face is dusky, livid or pallid; the eyelids twitch and are slightly separated. *Complete anesthesia* occurs in fifty to 120 seconds, averaging fifty-six. Its onset is denoted by a change in the respiration, which becomes slightly irregular and noisy. The pulse is quickened by about 30 per cent and is small. The blood pressure shows a large asphyxial rise (Kemp, 1897). The vasoconstriction diminishes the urine flow. The limbs are relaxed, but individual muscles exhibit clonic or epileptiform contractions. The pupils are almost invariably dilated. The face is cyanosed. Relaxation of the sphincters occurs rarely.

Operative Period.—As soon as this stage is reached, the gas is removed. The pulse at once becomes slower and fuller; the respiration also recovers rapidly; and the asphyxial symptoms disappear. The anesthesia lasts some twenty-two to thirty seconds after the gas is removed; and it is during this period that the operation must be performed. The total time between the beginning of the administration and complete recovery is therefore a hundred to a hundred and fifty seconds. The duration of the after-anesthesia increases with the duration of the administration. This may be prolonged to several minutes by giving the patient an occasional breath of pure air (every fifth inhalation); or by admitting a little air into the mask. The admission of air, however, makes the anesthesia uneven and unsatisfactory. *After-effects* are generally absent with short administrations. Sometimes the patients complain of giddiness, headache, lassitude and drowsiness. Nausea is exceptional.

Accidents are rare with short administrations (less than 1 to 5,000,000), because of the wide margin between the first danger sign (noisy and irregular respiration) and death. In patients with grave cardiac lesions, the pulse may become feeble and the respiration shallow before anesthesia is established. If the administration is continued too long in healthy individuals, the asphyxial phenomena become emphasized, with violent inspiratory, then forced expiratory movements; then shallow and intermittent and finally arrested respiration, in two to four minutes (Haggard, 1910). The violence of ordinary asphyxial convulsions is mitigated by the narcosis. Cyanosis is intense. The heart continues to beat for some time, so that *restorative measures* are generally successful. They should consist in artificial respiration, preferably with oxygen.

Contraindications.—Undiluted nitrous oxide should not be used in cardiac lesions, valvular or myocardial; in elderly patients especially with advanced arteriosclerosis or high cerebral pressure; and in operations on the brain. It is often ineffective in hysterical, obese, muscular or alcoholic patients (S. G. Davis, 1909).

Nitrous Oxide with Oxygen.—The respiratory disturbances, convulsive features and cyanosis produced by undiluted N_2O are purely asphyxial. If the gas is mixed with a sufficient proportion of oxygen (15 to 20 per cent), these asphyxial phenomena are absent, and the anesthesia can be prolonged indefinitely. With smaller percentages of oxygen, the symptoms are intermediate. The dilution of the gas with oxygen lowers its concentration in the blood to a corresponding degree, so that the narcotic action is not so prompt or deep. The concentration necessary for complete surgical anesthesia varies considerably in different individuals; most patients require at least 90 per cent of nitrous oxide and 10 per cent of oxygen; but 80:20 suffices sometimes, especially with morphine (Seevers and Waters, 1938). Ordinarily the 80:20 mixture inhaled at atmospheric pressure produces only confusion with incomplete loss of consciousness. Subanesthetic concentrations are definitely analgetic (Seevers, Bennett *et al.*, 1937); 20 per cent of nitrous oxide with 80 per cent of oxygen produces analgesia equivalent to 15 mg. of morphine (heat radiation test, W. P. Chapman *et al.*, 1943). *Morphine-scopolamine* greatly increases the efficiency of nitrous oxide, so that with these alkaloids, a mixture of 80 per cent with 20 per cent of oxygen at atmospheric pressure induces operative anesthesia (Kochmann 1914). Basal narcosis with barbiturates is serviceable.

Hewitt found that 6 per cent of oxygen is required to prevent the convulsive features and noisy respiration; 11 per cent to prevent lividity. Above 10 per cent, the reflexes and movements of the patient were more pronounced. Jackson, 1917, confirmed that the addition of more than 10 per cent of oxygen greatly delays or even prevents the loss of consciousness.

The *administration of the mixed gases* requires special apparatus for adjusting the two gases in any proportion. This is connected with a close-fitting mask. To hasten the anesthesia, the administration may be started with a mixture containing only 2 per cent of oxygen. This is gradually increased to 10 to 20 per cent. If the oxygen content is less than 13.7 per cent, by volume, the arterial oxygen tension falls below the dangerous asphyxial levels of 30 mm. (McQuiston *et al.*, 1943). Since asphyxial susceptibility varies unpredictably in different persons, Barach and Rovenstine, 1945, proposed that nitrous oxide should never be administered with less than 20 per cent of oxygen. If this proves insufficient, other anesthetic technics should be substituted.

Phenomena.—The primary symptoms are the same as with pure gas. The respiration is at first stimulated, so that the patient feels that he can breathe with less effort (Jackson, 1917). The *anesthetic stage* is usually reached in a few minutes. It is characterized by regular, calm, somewhat snoring respiration; slightly dusky face; and medium pupils. The pulse is moderately quickened; the blood pressure, somewhat high; the blood, rather venous.

Convulsive phenomena are absent. The reflexes and muscular tone are greatly decreased, but not abolished as with ether; the anesthesia is not so profound.

The stimulant effects of nitrous oxide on the respiration and circulation of dogs, like those of cyanide and lobeline, arise by reflexes, the respiration from the carotid body, the circulation from the aortic body (Comroe, 1938, 1939). Nitrous oxide has no action on other tissues and is harmless to them. Dogs anesthetized continuously for three days with a mixture of N_2O and oxygen recovered without any damage.

After-Effects.—When the administration is stopped, the patient awakens fully within two or three minutes. Nausea is exceptional, but more common than after short inhalations.

The *advantages* consist mainly in the greater comfort of the patient, the smaller danger and the absence of irritant side effects. The gas would therefore be especially indicated in renal and acute pulmonary diseases, or when the patient dreads the other anesthetics. Crile, 1910, claimed that it diminishes the danger of shock and infection. The *disadvantages*, contraindications and limitations were discussed under the undiluted gas. Its application is further limited by the rather shallow anesthesia, incomplete relaxation, high blood pressure and venosity of the blood, the expense of the gas and apparatus, inconvenience, and the need for specialized experience. Fatalities from the surgical use of nitrous oxide are perhaps fairly numerous, but reliable statistics are not available (*cf.* J. F. Baldwin, 1923). Prolonged inhalation of nitrous oxide with less than 15 per cent of oxygen leads to anoxic sequels similar to those described under carbon monoxide (Courville, 1936).

Nitrous oxide analgesia in obstetrics has been advocated as much safer than scopolamine-morphine "twilight sleep." It does not weaken the uterine contractions and has no bad effects on mother or child (Webster; Lynch; Davis, 1915).

Direct Narcosis and Anoxia.—Nitrous oxide depresses sensation directly, as shown by the analgesia and confusion in the presence of normal oxygen concentrations. Frogs which preserve their reflexes for hours when placed in pure hydrogen lose them promptly in undiluted oxide. The direct action is not sufficient, however, to produce complete unconsciousness, even with 2 atmospheres of nitrous oxide, if the partial pressure of oxygen is kept at the normal ⅕ atmosphere, 156 mm. (W. E. Brown *et al.*, 1927). It must therefore be concluded that the depth of the anesthesia depends mainly on anoxia; but that the nitrous oxide causes an additive analgetic depression, which permits a somewhat higher and safer oxygen ratio, enough to make the anesthesia practically feasible, and certainly less unpleasant.

No one has been able to confirm the statement of Paul Bert, 1880, that full anesthesia is produced in dogs by a mixture of 85 parts of N_2O and 15 parts of oxygen, at an excess pressure of ¼ atmosphere.

Anesthesia in dogs requires reduction of the oxygen of the inspired air to 11.5–3.6 volumes per cent, varying with individual animals and with the degree of anesthesia, which is generally light with 8 to 9.5 per cent of oxygen and moderate to deep with 4.9 to 5.2 per cent, the degree in a given animal increasing with the oxygen reduction (C. W. Greene and Currey, 1925). However, reduction of oxygen to less than 6 per cent soon produces unconsciousness even without nitrous oxide.

Blood Gases in Nitrous Oxide-Oxygen Anesthesia.—Nitrous oxide is very soluble in blood, to 45 per cent by volume (Bert). Greene *et al.*, 1925, found close to 23.3 volume per cent (18.9 to 26.8) in the blood during anesthesia, independent of the percentage inhaled (85 to 96) or the degree of anesthesia. On the other hand, the anesthesia showed a close inverse relation to the *oxygen* of the arterial blood, which ranged from 2.1 to 18.8 volumes per cent. Anesthesia was not satisfactory until the oxygen saturation had fallen to 80 per cent, from the normal of 92 per cent; but the anesthetic level of oxygen is somewhat higher than in pure anoxemia. Lucas, Henderson and Foster, 1931, also found the oxygen in nitrous oxide-oxygen anesthesia as 6 per cent (volume) in the arterial blood, 3 per cent in the venous blood, and 23 per cent in aerated blood. Anoxemia occurred with the inhalation of $N_2O:O_2::90:10$, even with the most careful administration.

Significant differences from typical narcotics are shown in the incompleteness of the narcosis if oxygen is adequate, and in the failure of nitrous oxide to narcotize *excised tissue* (muscle or heart) and *invertebrates.* On these, it acts merely as an indifferent gas. H. Wieland, 1922, therefore ascribed its effects (as also those of acetylene) to interference with oxidative processes in the central nervous system. Their partition coefficient is on the lipid side: 1.89 for N_2O; 1.39 for acetylene, contrasting with 4.5 for ether. Humphry Davy believed that nitrous oxide acts like oxygen on the blood, but Frankland showed that it is not decomposed. Nitrous oxide probably does not combine with *hemoglobin.* The *blood catalase* is diminished by nitrous oxide, as in other forms of anesthesia (Burge *et al.*, 1918).

High Pressures of Nitrous Oxide.—These are fatal above 3 atmospheres, even when inhaled with adequate oxygen. The symptoms consist in narcosis, convulsions and finally depressed respiration. The heart remains strong (Bock, 1913).

PREPARATION.—***Nitrous Oxide,** U.S.P. (Nitrogen Monoxide, Oxidum Nitrosum), N_2O, is a colorless gas; slight characteristic odor; somewhat sweetish taste. One volume dissolves in about 1.5 volumes of water. It is marketed, compressed into a liquid, in steel cylinders. It returns to the gaseous state when the pressure is released.

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MISCELLANEOUS HYDROCARBON ANESTHETICS

A large variety of volatile and soluble hydrocarbons have properties which would make them available for anesthesia, and a large number of these have been studied pharmacologically and clinically, as is indicated in the reviews of Seevers and Waters, 1938, and M. Kochmann, 1936; the latter also includes the toxicology of industrial fat solvents. Only those that have achieved some practical prominence will be considered here.

Experience has confirmed the prediction of Brown and Henderson, 1926: "The *methane series* will probably not yield an anesthetic gas." The useful agents are ether, olefine (ethylene) series, cyclic hydrocarbons, and halogenated compounds. *Volatility and solubility* favor the action, the volatility because it facilitates penetration into the lungs; the solubility because it favors quick absorption and tends to slow elimination.

ETHYLENE ANESTHESIA

Ethylene, $CH_2:CH_2$, is employed to produce gas anesthesia. Since its clinical introduction in 1923, mainly through Luckhardt, Carter and Lewis, the published reports have been almost uniformly favorable.

Historical.—The stupefacient phenomena of ethylene, and their resemblance to those of nitrous oxide, were recognized by the toxicologist L. Hermann in 1864. The effects on animals were described about as they are known today by Eulenberg, 1876, and Luessem, 1885, but it was not tried for surgical anesthesia on man. No further work on animals appeared for the next thirty-three years, when Malisoff and Egloff, 1919, did some further toxicity experiments. Meanwhile, it had been found by Crocker and Knight, 1908, that ethylene vapor in the high dilution of 1:2,000,000 has a toxic effect on plants, which was further studied by E. M. Harvey, 1914. This great toxicity for plants led Luckhardt and Carter, 1923, to study its effects on animals; its low toxicity but rapid action on animals led them and their co-workers (Luckhardt and Lewis, 1923) to develop its successful clinical application. Nearly at the same time and in ignorance of their work, W. E. Brown, 1923, also reinvestigated the effects of ethylene on animals and men, with more knowledge of the older work, and with a direct view to surgical anesthesia; but he did not proceed to the clinical application.

Anesthetic Effects.—Ethylene is an aliphatic narcotic with relatively low potency, but with rapid action and recovery, due to its high volatility. Its effects may be conceived as analogous to a rapid ether anesthesia; but because of their rapidity, the phenomena appear more similar to those of nitrous oxide. It acts more powerfully and more promptly than the latter. Full anesthesia, which requires 90 per cent (volume) of ethylene and 10 per cent of oxygen, is established in about half the time required for the ordinary nitrous oxide-oxygen induction; the anesthesia and relaxation are deeper, and adequate for major operations; the recovery is more rapid, the patient being usually awake with clear mind within two minutes after discontinuance of the anesthetic. The percentage of ethylene may be gradually reduced toward 80 per cent in prolonged anesthesia. The rapid action and recovery demand close attention on the part of the anesthetist.

Mechanism of Action.—As with the other aliphatic narcotics, this appears to be connected with a high partition coefficient (= 13.2; Luckhardt and Carter, 1924).

Effective Concentration.—Mammals are generally only slightly depressed by mixtures containing 80 to 85 per cent of ethylene diluted with oxygen; with 90 per cent, the anesthesia becomes complete in twenty to thirty minutes (Luckhardt and Carter, 1923); 25 to 35 per cent produces analgesia; consciousness is sometimes lost with 40 per cent, generally with 50 to 60 per cent (Seevers and Waters, 1938). Continued inhalation of 85 to 86 per cent is slightly toxic, with slow fall of blood pressure and respiration; 89 per cent is quickly toxic; 93 to 95 per cent is acutely fatal (W. E. Brown and Henderson). Frogs are anesthetized by the 85 per cent mixture in twenty minutes, while 85 per cent illuminating gas produces no marked effects in thirty minutes (Luckhardt and Lewis, 1924).

Special Phenomena.—The *induction* is not disagreeable to the patient. The gas has a rather unpleasant odor, but it is not noticed after a half-dozen inhalations, because of the mental confusion. Talking and excitement are relatively slight and often absent. Analgesia occurs before the full anesthesia.

During established anesthesia, the respiration is practically normal. The excitability of the medullary centers is not lowered; they tend rather to be slightly stimulated by the lowered oxygen concentration, and hemorrhage is accordingly somewhat increased during the anesthesia; but the asphyxia is slight and does not progress to cyanosis. The respiration is slow and regular and the pulse scarcely changed. Sweating and salivation are slight or absent, and the temperature fall is relatively slight. Renal efficiency (phthalein excretion and saline diuresis) is not impaired; pulmonary irritation also appears to be absent. Postanesthetic vomiting is only half as frequent as with ether (30 per cent of the ethylene anesthesias as against 77 per cent of ether anesthesias, in the series of Luckhardt and Lewis), and when it occurs it is less severe and less persistent. Gas pains, in the same series, occurred in only 4 per cent of the ethylene, against 37 per cent with ether; they are no more troublesome than after local anesthesia. In obstetric use, it does not materially reduce the uterine contractions, and permits prompt respiration to the delivered child (Heaney, 1924).

Morphine is not required even for deep anesthesia, but it facilitates the administration, and permits the use of somewhat lower concentrations (Luckhardt and Lewis, 1924).

Respiration, Circulation and Temperature.—In animals, the CO_2 production is depressed only in proportion to the muscular relaxation. The respiratory center is not depressed by anesthetic doses, the rate and depth being increased in proportion to any anoxemia. The *blood pressure* rises about 10 mm., showing that the vasomotor center is not injured. The temperature falls but little. *Excised frog or mammalian heart* is not injured by saturating the perfusion fluid with ethylene (Bouckaert, 1924).

Digestive Tract.—The gastric secretion and motility (emptying time) are depressed clinically, but less than with ether (R. L. Johnson and Ivy, 1926). In animals also, when ethylene is administered to produce ordinary surgical anesthesia, the gastric movements are slightly depressed; but the movements of the small and large intestines are stimulated, in contrast to other inhalation anesthesias. In deep anesthesia, these are also highly depressed (Miller and Plant, 1925). Excised intestines of rabbits respond with slight and transitory decrease of tonus and some increase of amplitude of the contractions (S. A. Peebles and Phatak, 1934).

Hydrogen-Ion Concentration of the Blood.—Ethylene lowers the actual alkalinity of the arterial blood considerably less than ether or chloroform, and about the same as nitrous oxide. If anoxemia occurs, this causes a preliminary alkalosis (always with nitrous oxide; Leake, 1924).

Fatalities.—None are likely to occur with clinical concentrations. If the concentration is pushed much beyond 90 per cent in animals, death results mainly from anoxemia, *i. e.*, by respiratory failure. The circulation is not affected directly by the ethylene, so that resuscitation is relatively easy. *Impure ethylene*, of peculiar odor, produced cyanosis, imperfect relaxation, and subsequent prolonged emesis (Luckhardt, 1924).

The *advantages over ether* are principally: the easier, more pleasant, prompter and safer induction; the diminution of emesis and gas pains; the more rapid recovery; and the minimizing of renal and pulmonary irritation. *Advantages over nitrous oxide* consist in the practical absence of asphyxia; the deeper anesthesia and more complete relaxation; the lesser excitement and struggling; and the prompt recovery.

Disadvantages.—The principal drawback is the explosiveness of the ethylene-oxygen mixture, which demands the careful exclusion of electric sparks (static or other), open flames and cautery. This precaution is equally essential, however, with ether vapor: W. Bourne, 1934, found records of twenty ethylene explosions in operating rooms; and in the same period, thirty-nine explosions of mixtures of nitrous oxide, ether and oxygen (but this would make the percentage of ethylene explosions much higher than for the ether mixtures, since the latter were doubtless administered much more frequently).

Ethylene gas in encephalography appears to have some advantages over air, in that the subsequent headache is less severe and much less persistent (H. Newman, 1937).

Plants.—Ethylene gas is used to hasten the maturation of fruits and vegetables; it is indeed said to be produced in these processes.

***Ethylene, U.S.P.** (Aethylenum), contains 99 per cent, by vol., $CH_2{:}CH_2$. A colorless gas, somewhat lighter than air, of slightly sweet odor and taste. Sol. in water (1:9) at 25° C. Usually furnished in compressed form in metallic cylinders. Inflammable and explosive.

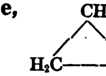
OTHER OLEFIN GASES

The introduction of ethylene anesthesia gave impetus to the study of other gases of the series $C_n H_{2n}$, but they are probably not sufficiently valuable (Seevers and Waters, 1938). The literature is cited by L. K. Riggs, 1925. The experiments of the latter on rats show that the activity of the lower members increases in nearly geometric ratio; *i. e.*, the concentration of gas required to produce anesthesia is, for ethylene, 90 per cent (volume); for propylene, 40 per cent; for butylene, 20 per cent; and for amylene, 6 per cent. With butylene and amylene undesirable side actions appear (exaggerated excitement stage; respiratory disturbances).

Diethylene.—Intravenous injection of 0.05 cc. into decerebrate cats raises blood pressure by stimulation of the vasomotor center. It has little effect on the respiration, heart or blood vessels directly (Bijlsma and van Esveld, 1929).

Propylene gas ($H_3C.HC{:}CH_2$) acts similarly to ethylene, but is more powerful, so that 50 per cent (volume) induces unconsciousness in two minutes, in man, and concentrations of 37 to 40 per cent suffice for anesthesia. This would permit considerable economy in oxygen as well as in the anesthetic. Its administration is not unpleasant, and recovery is rapid. In animals, toxic phenomena appear slowly with 65 per cent, rapidly above

70 per cent (W. E. Brown, 1924; Halsey, Reynolds and Prout, 1926). In dogs and cats, propylene may cause *ectopic ventricular beats*, the number increasing with the concentration of the gas. They disappear when the administration is stopped (C. R. Caine and Reynolds). Repeated prolonged propylene anesthesia of mice results in less visceral degeneration than with ethylene, and about the same as with nitrous oxide and ether. *Isolated uteri and intestine segments* are little affected by either propylene or ethylene. *Isolated frog and turtle hearts* survive longer in oxygen containing anesthetic equivalents of propylene than of ether (C. Reynolds, 1926).

Cyclopropane,  , an isomer of propylene, was proposed by G. H. W. Lucas and Henderson, 1929, as a promising anesthetic. It has been used clinically with good results in a considerable number of anesthesias, especially in Wisconsin and Montreal (Waters and Schmidt, 1934; W. Bourne, 1934; review, Council on Pharmacy and Chemistry, 1941, J.A.M.A., *116*:2502). Its actions and uses are intermediate between those of ether and ethylene, but its administration requires special experience, since the signs of anesthesia differ from those of other anesthetics. Its chief *advantage* is the quick and pleasant induction and the minimal side effects, so that it is preferred by patients. The most serious *disadvantage* is the liability to cardiac arrhythmia and ventricular fibrillation, which is even greater than with chloroform. Sympathomimetic drugs should not be employed with it. A number of explosions have occurred in its use; these are greatly feared, although its explosibility is perhaps no greater than with other anesthetic-oxygen mixtures.

***Cyclopropane,** U.S.P. (Trimethylene), is a colorless gas, with a characteristic not unpleasant odor, boiling at −32.9° C., inflammable and explosive similarly to ether (explosive range in air, 3 to 8.5 per cent; in oxygen, 2.5 to 50 per cent). It has a high oil:water partition coefficient (64.4 at 35° C., as compared with ether, 2.5; ethylene, 13.2; acetylene, 2.1; Henderson and Lucas, 1930). It is soluble in water to 20.4 volumes per cent, in oxalated blood to 45.7 per cent; the corpuscles dissolve 2½ times as much as the plasma. It is likely to polymerize on standing and to contain propylene and cyclohexane as impurities, but this is not practically important.

Course.—Unconsciousness occurs in one or two minutes. Excitement is present in only 3 per cent. Recovery is rapid, but slower than with other gases. The most important difference from ethylene and nitrous oxide is that it produces anesthesia in much lower concentration, 15 to 25 per cent by volume, so that the oxygen intake is easily kept at the normal level. The muscular relaxation is therefore much better than with nitrous oxide, although not so complete as with ether. Postanesthetic nausea, however, is more frequent than with nitrous oxide. Pulmonary complications are no more frequent than with the other anesthetics. It does not appear to cause liver degeneration. It is administered in a closed system with carbon dioxide absorption, to economize the gas. The oxygen is maintained at 20 per cent. There is no cyanosis, and the criteria of other anesthetics do not apply. The decisive danger signal is cardiac irregularity, extrasystoles, bradycardia or tachycardia. Premedication interferes with these signs; but ordinary doses of morphine reduce the concentration required for a given level of anesthesia by 10 to 12 per cent (Seevers and Waters).

Effective Concentrations.—Prolonged inhalation of 3 to 5 per cent produces analgesia; 6 per cent causes unconsciousness in many subjects (Seevers, Bennett *et al.*, 1937). In clinical cases the concentration in the mask averaged 7.4 volumes per cent for mild anesthesia, 13.1 per cent for the majority of abdominal operations, 23.3 per cent for deep anesthesia, 43 per cent for arrest of respiration. With dogs, complete muscular relaxation occurs with 20 to 25 per cent; respiratory paralysis usually with 40 per cent; cardiac arrhythmias with 46 per cent, and cardiac paralysis with 60 to 80 per cent, the latter notwithstanding artificial respiration and adequate alveolar oxygen tension (Seevers, Meek *et al.*, 1934). The blood concentration with dogs averaged 16.8 mg. per 100 cc. for abdominal relaxation, 20.6 mg. for loss of lid reflex, 25.5 mg. for costal paralysis, 28.2 mg. for arrest of respiration (B. H. Robbins, 1936, 1937).

Respiration.—Cyclopropane does not irritate in clinical concentrations, and does not produce induction disturbances. Anesthetic concentrations depress the respiration, progressing to arrest with toxic dosage (Waters). The CO_2 content of the blood and tissues rises accordingly. Statistics indicate a low incidence of pulmonary complications (Burford, 1938). Massive atelectasis may occur by rapid absorption of oxygen behind localized bronchial obstructions (Coryllos and Birnbaum, 1932; O. R. Jones and Burford, 1938). *Salivation* is somewhat greater than with nitrous oxide or ethylene, but less than with ether or chloroform.

The blood pressure is practically unchanged in smooth anesthesia, but may rise through asphyxia or reflexes. The blood vessels are relaxed and capillary bleeding appears to be increased.

Cardiac irregularities develop readily under certain conditions, although full anesthesia can generally be obtained without arrhythmia or other electrocardiographic change. In the absence of other medication they set in about the time when respiration ceases, with concentrations of 35 per cent or higher in dogs (Seevers *et al.*, 1934); but they occur even when the blood is fully oxygenated by artificial respiration, and in perfused hearts they are proportional to the dissolved cyclopropane; this, therefore, *acts directly* (W. V. Lee *et al.*, 1943).

The irregularities in intact animals generally disappear promptly when the concentration of the cyclopropane gas mixture is decreased. They do not render the heart more subject to overdistention by saline injection, indicating that it is not seriously injured (Meek and Volpitto, 1936). *The susceptibility to cyclopropane arrhythmia* is increased by anoxia, by morphine (cyclopropane tends to augment the morphine bradycardia in dogs; Robbins *et al.*, 1939); and particularly by epinephrine and related sympathomimetic amines. Partial protection is furnished by atropine, barbiturates, procaine, quinine, quinidine and other cardiac depressants (J. H. Baxter and Robbins, 1939).

Injection of epinephrine during light cyclopropane anesthesia produces ventricular tachycardia which readily passes into ventricular fibrillation. This is less liable to occur in deep anesthesia; it does not occur in decerebrated dogs. C. R. Allen, Stutzman and Meek, 1940, suggested that cyclopropane increases the irritability of the heart by sympathetic stimulation through a brain center above the pons. *The same effect* is produced by arterenol, epinine, kephrine, and cobefrine; not by ephedrine, propadrine, benzedrine, synephrine, neosynephrine (O. S. Orth *et al.*, 1944). Brief ventricular fibrillation is easily reversible. It is prevented by procaine, 16 mg. per Kg. by vein; but this is ineffective after the fibrillation has set in, even if injected intracardially within thirty seconds (Stutzman *et al.*, 1945). Barbiturates are not very effective (Meek and Seevers, 1934).

Nausea and vomiting are not frequent. In 10,000 clinical anesthesias recorded by Waters, these symptoms occurred in 56.5 per cent of ether administrations, 39 per cent of cyclopropane, 33 per cent of ethylene, 23 per cent of nitrous oxide. *Intestinal motility* has given somewhat discordant results. In fistula dogs, Weisel, Youmans and Cassel, 1938, observed decrease of tonus and inhibition of movement, returning to normal promptly after discontinuing inhalation. Burstein, 1938, reported increased tonus and contractions in light anesthesia; in deep anesthesia the contractions were diminished, but the tonus remained high. Excised segments from rabbits responded with increased tonus and contractions (Peebles and Phatak, 1935). The *urine output* is decreased during anesthesia with compensatory increase some hours later, as with ether and ethylene. Inhalations lasting an hour and repeated daily did not impair the *liver* function tests or produce any histological changes in dogs (Raginsky and Bourne, 1934).

Fate.—Cyclopropane is not converted into its isomer propylene in the animal body. It is absorbed and eliminated more rapidly than ethylene if the gases are injected under the skin or into the peritoneum (Seevers, de Razio and Evans, 1935).

Methyl (mono, di and tri) cyclopropanes are unsuitable for anesthesia, as they produce more cardiac irregularity and fall of blood pressure (V. E. Henderson and MacDonald, 1937; W. A. Lott *et al.*, 1938).

ACETYLENE

Anesthesia by the purified gas, HC:CH, has not become popular, perhaps because its advantages do not appear to be sufficiently great to balance the disagreeable odor. Its introduction, like that of ethylene, resulted directly from experiments undertaken primarily for theoretical "academic" purposes (review, Seevers and Waters, 1938).

Clinical Application.—Gauss, 1923, used a gas mixture of 40 per cent (by volume) of acetylene and 60 per cent of oxygen, flavored with oil of pine. The effects are similar to those of ethylene. It is necessary to employ a purified gas, as ordinary acetylene contains toxic impurities, such as H_2S (Wefers, 1917), which were largely responsible for the effects described by earlier observers.

Mechanism of Action.—Wieland, 1922, believed that nitrous oxide and acetylene differ from ordinary narcotics in that they do not appear to anesthetize organisms and processes that do not require free oxygen (ascaris; the contraction phase of muscle, and so forth). He also found that acetylene anesthesia greatly reduces the carbon dioxide production in higher animals.

Anesthetic Action on Animals.—The susceptibility appears to vary rather widely (Wieland). C. N. Jordan, 1923, required about 80 per cent for dogs. He emphasized the rapid recovery, and the absence of after-effects, even with a four hour anesthesia. The *blood pressure* rises and the pulse is slowed by stimulation of the vasomotor and vagus centers, even when ample oxygen is present. Spinal reflexes are depressed (Bollert, Eichler and Hildebrandt, 1927).

Effects on Man.—B. M. Davidson, 1925, found that human subjects were rendered unconscious in five to six minutes by 33 to 35 per cent; 30 per cent was not sufficient. Repeated inhalations (three times within a week) decreased the susceptibility; while 33 per cent acetylene abolished consciousness in six minutes at the first inhalation, it required nine minutes at the second, and more than thirty-three minutes at the third. A similar diminution was produced in the rapidity and degree of the minor disturbances of the psychic functions by lower concentrations, which she studied in some detail. Inhalation of 10 per cent of acetylene is used for *determining the cardiac output* (Grollman, 1929); 4 per cent ethylene is used similarly. These have some advantage over the ethyl iodide method of Richard, 1926.

VINYL ETHER (VINETHENE)

The actions of divinyl oxide, CH_2:CH.O.CH:CH_2, are intermediate between those of ethylene and ordinary ethyl ether. It differs from the latter chiefly by greater rapidity and brevity of action, due largely to its greater volatility. It is a colorless fluid of ethereal odor, boiling at 28.3° C., specific gravity 0.77 at 20° C. Anesthesia is promptly induced and easily maintained, with quick recovery. The rapid course requires special caution in its administration, but renders it useful for short operations, such as extraction of teeth, reduction of fractures, obstetric operations; and for induction to other anesthetics. The excitement is much less than with ethyl ether; salivation is moderate, but persists even after atropine; nausea and vomiting occur in about 5 per cent of the patients; muscular relaxation is satisfactory, although not so complete as with ethyl ether; the blood pressure is unchanged; postoperative complications are infrequent. The liability to liver injury is between ether and chloroform, and must be guarded against, although it has not been reported clinically (Ravdin, Eliason *et al.*, 1937). It may occur in prolonged inhalation in animals, even when the oxygen supply is abundant (Goldschmidt *et al.*, 1934;

von Brandis). The explosion hazard is about the same as for ethyl ether. Vinyl ether may be administered for short operations by dropping on an open or semiclosed mask; if the administration exceeds forty-five minutes, it is better to give it with oxygen. Normal respiration is the best guide to its use. Eye signs are not reliable. If cyanosis should develop, or if anesthesia is in any way unsatisfactory, the vinyl ether should be stopped and another anesthetic substituted.

Anesthesia requires a *blood concentration* of $\frac{1}{7}$ that of ethyl ether for man, $\frac{1}{4}$ for animals (28 mg. against 116 mg. per 100 cc.); the fatal concentration is about half that of ethyl ether (68 mg. against 155 mg.); Goldschmidt *et al.*, 1934. This would give a wider margin of safety, but this is offset by the lower total concentration, especially in view of the rather wide variability of response (Ruth). Several clinical deaths have been reported. In dogs the anesthesia is complicated by disturbing running movements. The *intestinal tonus and movements* are decreased in all stages of the anesthesia (fistula dogs; Burstein, 1938). The excised intestine of rabbits may react with increased tonus (Peebles and Phatak, 1934).

Historical.—Divinyl ether was first investigated as a possible anesthetic agent by Leake and associates, 1933 and 1934, and has been applied clinically especially by W. Bourne, 1934 and 1935; S. Goldschmidt, 1934; Waters, 1934; Shipway, 1935; and Lundy, 1935. A review by the Council on Pharmacy and Chemistry is published in the Journal of the American Medical Association, 1937, *109*:656.

Vinyl Ether, U.S.P. (Divinyl Oxide, Vinesthene), contains about 4 per cent of alcohol and not more than 0.025 per cent of harmless preservative phenyl alphanaphthylamine to delay polymerization. Slightly sol. in water, readily in alc. and in oils. It should not be used for anesthesia if the original container has been opened longer than twenty-four hours. Decomposition products include formic acid and formaldehyde.

Cyclopropyl vinyl ether ("*Cyprethylene Ether*"), administered by inhalation, approximates the anesthetic potency of divinyl ether and of chloroform. The heart activity is normal with anesthetic concentrations. Functional liver damage was demonstrable in monkeys (J. C. Krantz, Evans *et al.*, 1942).

Isopropenyl vinyl ether ("*Propethlene*") approximates chloroform in potency and lowers blood pressure, but does not produce hepatic or other visceral injury (Krantz, Carr *et al.*, 1943).

Isopropenylmethyl ether ("*Isoprome Ether*") produces good anesthesia in animals, with complete muscular relaxation (Krantz, Carr *et al.*, 1943).

Propenyl ethyl ether produces effective anesthesia in animals with relatively high factor of safety, but irritates the upper respiratory tract (Krantz, Carr *et al.*, 1943).

Dimethyl Ether.—W. E. Brown, 1924, found 65 per cent (by volume) to produce anesthesia, but it is unpleasant to take and the recovery is slow.

n-Propyl methyl ether compares favorably with ethyl ether in animals (J. C. Krantz, Evans *et al.*, 1946).

Methane.—W. E. Brown, 1924, found that this has a narrow zone of safety; unconsciousness occurs with 87 per cent (by volume), and death with 90 per cent. Its effects are mainly asphyxial.

Methyl Formate Vapor.—With guinea pigs, 0.15 per cent produces nasal and conjunctival irritation, retching, narcosis and death, apparently by pulmonary irritation; autopsy shows congestion and edema of the lungs and hyperemia of the liver, kidneys and brain surface. Death occurs in two and one-half hours in 1 per cent, in one-half hour in 5 per cent vapor (Schrenck, Yant *et al.*, 1936).

Ethyl acetate ("acetic ether") inhalation produces acute pulmonary edema and congestion of the liver and kidneys. Chronic poisoning results in secondary anemia, leukocytosis, and cloudy swelling and fatty degeneration of the viscera (Blina, 1933).

Iso-amyl acetate ("Banana oil solvent") is used as a cellulose solvent. It causes local irritation of the eyes, upper respiratory tract and other exposed tissues, but it is not dangerous systemically (Hamilton, 1915, 1917; Smyth and Smyth, 1928). *Secondary amyl acetate* appears to be more irritant, narcotic and toxic (F. A. Patty *et al.*, 1936).

"Methyl cellosolve" has been reported to produce encephalopathy and profound depression of the bone marrow or granulopenic anemia in exposed workers (Parsons and Parsons, 1938).

Lacquer Solvents.—H. F. Smyth and Smyth, 1928, who investigated the toxic effects of the inhalation of these vapors, group them as to safety as follows: (1) Usable safely in concentrations ordinarily attained in brushing and spraying, or sometimes higher: ethyl acetate, amyl acetate, perhaps butyl acetate. (2) Safe in ordinary concentrations, but to be increased only with caution: gasoline, turpentine, xylol. (3) The present spray concentrations cannot be safely exceeded: toluol and butyl alcohol. "*The Toxicity of Industrial Solvents,*" E. Browning, 1938, contains a review of all classes of these solvents, prepared on behalf of the British National Research Council. They are also reviewed by von Oettingen, 1942, and M. Kochmann, 1938.

HALOGENATED ANESTHETICS

The introduction of halogen atoms increases the anesthetic potency and the toxicity of the aliphatic narcotics, up to nearly complete replacement of all the H atoms, but diminishes again somewhat if no H remains. The toxicity also increases with the length of the carbon chain. Chloroform, $CHCl_3$, was discussed with ether; carbon tetrachloride with the anthelmintic agents (see Index).

Data on the *comparative toxicity* of the chlorine derivatives of the aliphatic series are given by Barsoum and Saad, 1934, and by Alice Hamilton, 1943. The chlorine derivatives of cyclopropane were investigated by V. E. Henderson, 1938.

Fate.—Methyl chloride, bromide and iodide are decomposed in the body into methanol and the halogen acid.

Severe methanol poisoning may result from prolongep exposure to subanesthetic concentrations. The corresponding ethyl compounds form ethanol. *Di, tri and tetra halogen compounds* are virtually not decomposed. The decomposition of various *bromine-containing anesthetics* in the body is discussed by Lucas, 1928, and Glaser, 1928.

Ethyl Chloride.—On account of its high volatility, the anesthesia appears and disappears promptly, and is therefore especially adapted for minor surgery. It has the same *dangers* as chloroform: relatively small doses may cause sudden stoppage of the heart, though less frequently than chloroform. Larger doses paralyze the heart muscle directly; and are even more dangerous than chloroform, because of the extreme suddenness and rather indefinite signals (E. D. Brown and Large, 1905; Wood, 1910). Its main *advantages* consist in the rapidity with which anesthesia is induced; in the consequent absence of struggling, excitement and unpleasant sensation; in the prompt and complete recovery. Its administration is often followed by headache, nausea, vomiting, and sometimes collapse. The muscular relaxation and abolition of reflexes are incomplete, and a little experience is required to recognize the proper time for operating. It has occasionally failed in alcoholic patients. Administering ethyl chloride by his special closed-circulation apparatus, D. E. Jackson, 1916, found its effects to be intermediate between those of nitrous oxide and ether. The concentration of ethyl chloride in the blood and tissues during narcosis was investigated by Camus and Nicloux, 1908, and E. Frey, 1912.

The main use of ethyl chloride is for *local anesthesia*, freezing the tissues by a fine spray of the liquid; the tube is held about 3 feet away. The impossibility of dissecting the frozen tissues restricts its use to simple incisions (opening boils); the analgesia is imperfect, and the thawing rather painful.

Ethyl Chloride, U.S.P. (Monochlorethane), C_2H_5Cl, is a colorless, extremely volatile liquid, of sharp, sweet taste and peculiar odor. Inflammable. Boiling point, 12° to 13° C. Sparingly sol. in water, readily in alc. or eth. Dispensed in special glass or metal containers. Used for freezing and for general anesthesia.

Methyl chloride boils at —24° C. It has been tried for anesthesia by inhalation and as a refrigerant spray, but the latter may produce vesication. Its chief use is in domestic refrigerators, and poisoning may be produced by the escape of the vapor. H. M. Baker, 1927, reviewed twenty-one cases. The *symptoms* consisted in vertigo, drowsiness, anorexia, slight nausea, visual disturbances from slight blurring to diplopia, but without changes in the eye ground. There is also a characteristic gait. Formate is found in the urine. The breath for several days has a peculiar odor, probably either methyl alcohol or acetone (Weinstein, 1937). A further group of twenty-nine cases, ten of them fatal, was reported in Chicago by Kegal, McNally and Pope, 1929. *Postmortem examination* showed pulmonary edema, cardiac dilatation, degenerated areas in the liver and kidneys, and scattered petechial hemorrhages. A special committee of the American Medical Association made recommendations to decrease the hazards (J.A.M.A., *94*:1832), which appear to have been fairly effective. The minimal *fatal concentration* for guinea pigs, with seventy-two hours of exposure, is 75 parts per million of air (J. L. White and Somers, 1931). Daily exposure of dogs and monkeys to 500 ppm becomes extremely dangerous within two weeks (W. W. Smith and von Oettingen, 1947). Eight cases of industrial poisoning are reported by W. D. McNally, 1946. Poisonous effects from absorption into food and drink are not likely, as the marked taste would prevent the consumption of toxic quantities (Yant, Shoaf and Chornyak, 1930).

Allyl chloride is the most toxic of the halogenated aliphatic hydrocarbons, its vapor being strongly irritant and causing death by pulmonary irritation. Animals that survive recover completely (E. M. Adams, Spencer and Irish, 1940).

Vinyl chloride was investigated by Patty, Yant and Waite, 1930.

Ethyl bromide resembles ethyl chloride closely (Weber, 1906), but has a higher boiling point, 38° to 40° C. It is used for short anesthesia, or rather analgesia. It must not be pushed to the disappearance of reflexes, since the respiration is paralyzed about the same time. The zone of safety is therefore narrow. Pain is abolished before consciousness, and the operation must be made before consciousness is entirely gone. The proper time for operating is somewhat difficult to choose, and the drug is dangerous in unskilled hands. With experience, the danger seems to be slight. The proper amount (for adults, 8 cc.; for children not more than 1 cc. per year) is poured on a folded towel or cone, and administered to the exclusion of air, until the proper degree of anesthesia is reached. It is then removed. It is only suitable for short operations (tonsillectomy, and so on). The administration requires twenty to forty seconds; the anesthesia lasts about two minutes. Recovery occurs at once. Inhalation of ethyl bromide in high concentration (6 to 18 per cent) for short periods produces acute pulmonary congestion and edema in animals; low concentrations (0.32 to 2.4 per cent) inhaled for a longer period produce the same effects, and also acute parenchymatous nephritis (C. P. Waite and Yant, 1928). It should be protected from light and heat. After a bottle has been opened, the contents cannot be used again, as they deteriorate rapidly. The drug must not be confused with *ethylene bromide* ($C_2H_4Br_2$), which is more toxic.

Ethyl iodide also resembles ethyl chloride in action (Weber, 1906), but boils at 72° C. It is inhaled for determining the cardiac output (Richard, 1926). Its excretion after inhalation of 1 to 3 cc. was studied by Blumgart, Gilligan and Swartz (1931): About 45 per cent is exhaled during the inhalation, and a further 9 per cent during the first two hours afterwards; 31 per cent is excreted by the urine (85 per cent of this in the first twenty-four hours); the remaining 15 per cent is presumably eliminated by the intestines, skin and sputum. Within therapeutic limits, the percentage retained is independent of the quantity inhaled.

Methyl bromide is a gas at ordinary temperature, boiling at 45° C. It is supplied liquefied by pressure. The vapor does not explode readily. It is used as a *fumigant* for the extermination of lice and bedbugs, and for the eradication of certain insects in food materials. Some remains tenaciously adsorbed in the latter, but not enough to produce deleterious effects (H. C. Dudley and Neal, 1942). It is also employed extensively as refrigerant, as fire extinguisher, and as methylating agent in chemical industry. It is a highly toxic and insidious agent and must be handled cautiously (review and bibliography, von Oettingen, 1946; industrial poisoning, H. Wyers, 1946). In animal experiments it is more toxic than methyl chloride, producing local irritation, pulmonary edema and pneumonia. Longer exposures to lower concentrations cause excitement, convulsions, paralysis, with cerebral congestion and visceral degenerations. *Industrial poisoning* is characterized by peculiar nervous after-effects. The immediate relatively slight narcotic symptoms pass off promptly, but are followed after several hours or even days by motor, sensory and psychic disturbances—aphasia, amblyopia, and so forth, lasting usually about two weeks and then regressing slowly; or they may persist for years. Some patients develop an epileptiform syndrome; others show congestion of internal organs (Duvoir, Fabre and Layani, 1937; R. N. DeJong, 1944). Animal experiments show that the methyl bromide has largely or entirely disappeared before these effects develop (E. Glaser, 1928). They are apparently due to neurodegenerations similar to those of carbon monoxide and manganese, perhaps from decomposition products.

Bromoform ($CHBr_3$) is not sufficiently volatile to be used as an anesthetic. It is employed as an antispasmodic in whooping cough, but is of doubtful value. It is a heavy liquid, resembling chloroform. Slightly soluble in water; miscible with alc., chlorof., eth., and fixed or volatile oils. Slightly volatile, not inflammable. Dose, 0.2 cc., on sugar dissolved in alcohol and glycerin.

Trichloroethylene, $CHCl{:}CCl_2$, a highly volatile, noninflammable liquid, boiling at 88-90° C., produces prompt analgesia and anesthesia on inhalation, resembling chloroform, but more rapid in action and less potent. It is used as analgetic (1 cc. self-inhaled from gauze until the odor has disappeared, three or four times daily, for four to six weeks) to relieve the pain of trigeminal neuralgia (M. A. Glaser, 1931), angina pectoris (where it acts solely as analgetic, and has no effect on the coronary vessels; Krantz *et al.*, 1938), and migraine (Geiger and Goodman, 1937).The patient should recline, since there is sometimes vertigo and drowsiness, although not general anesthesia. This dosage appears to be practically nontoxic and may be repeated if necessary, but generally not more than 4 cc. in a day. Patients should be warned against overdosage and addiction.

Its use originated in an observation of Plessner, 1915, that accidental inhalation in industries, where it is used as fat and varnish solvent, produced bilateral loss of sensation of the trigeminal distribution. It appears now that this is due to neuritis, and not to functional anesthesia. Following a suggestion of Oppenheim, 1915, Plessner applied it to trigeminal neuralgia.

Inhalation of 1 to 2 cc. from gauze produces a momentary choking sensation, then dizziness, confusion, inebriation and markedly diminished sensitivity to pain, exactly as in the analgetic stage of other inhalation anesthetics. It is not confined to the trigeminal distribution. Tactile acuity (tested by von Frey hairs) is not decreased (Council on Dental Therapeutics, 1931). *Addiction* to trichlorethylene, for inebriation and elation, has been reported in several cases. Eichert, 1936, described two patients who finally used 120 to 180 cc. within a few days, with marked mental changes, which cleared up on discontinuing. Other cases are reported by Jordi, 1937, and by N. K. Rickler, 1945.

General anesthesia by trichloroethylene (under the name of "*trilene*") became rather popular in England. The claimed advantages are ease of administration, absence of local irritation and of superficial oozing from cut surfaces, and relative safety (C. L. Heiver, 1942), but acute fatalities are fairly frequent (A. R. Hunter, 1944). It requires more oxygen than ether. Too rapid administration causes respiratory depression (H. F. Griffiths, 1942). It is somewhat more difficult to achieve complete muscular relaxation. It does not usually produce significant *electrocardiogram* changes clinically, but larger doses cause marked slowing of the heart rate, ectopic beats and changes in the P and T waves in animals (Mallach *et al.*, 1943). Disturbed automaticity is sometimes seen in man (Waters *et al.*, 1943). Its pharmacology was investigated by Joachimoglu, 1921.

Its clinical administration by closed apparatus may result in persistent trigeminal and other *cranial palsies*, attributed to toxic degradation products, dichloroacetylene, phosgene and carbon monoxide, formed by interaction with the soda lime of the absorber system. Dichloroacetylene produces encephalitis in rabbits (J. H. Humphrey and McClelland, 1944; S. Carden, 1944).

Chronic industrial poisoning with trichloroethylene results in some local irritation and dermatitis (L. Schwartz, 1939), and in systemic effects, headache, vertigo, anoxemia and nervous disorders, due to severe polyneuritis, including paresthesia and disturbed sensibility in the extremities (H. J. Pearson, 1934), paralysis of the trigeminal nerve, disorders of vision by optic nerve atrophy, and permanent blindness from retrobulbar neuritis (Isenschmidt and Kunz, 1935). These neuritic phenemena are probably caused by impurities.

Chronic Effects on Rats.—Acute exposure to 0.2 per cent of vapor produces slight narcosis; 0.3 to 0.5 per cent results in deep anesthesia. With chronic exposure (six hours per day, five days per week, up to six months), 0.3 per cent generally proved fatal in less than six months; with 0.2 per cent and less, the rats survived (as also did dogs), without noticeable deleterious effects. Their growth curves were similar to those of the control animals, and no histologic abnormalities were found in the liver, kidneys, lungs or other organs (H. Taylor, 1936).

Trichloroethylene, U.S.P., is a clear, colorless, volatile liquid, of specific gravity 1.46, with an odor similar to that of chloroform. A small amount of ammonium carbonate may be added as preservative. On exposure to air it forms small amounts of the irritant phosgene, hydrochloric acid and dichloracetyl chloride. It is very soluble in alcohol, practically insoluble in water, soluble in organic solvents. It is generally sealed in thin glass tubes containing the usual inhalation dose, 1 cc. Oral administration of 0.25 Gm., in gelatin capsules, three times daily has been suggested (Seelert, 1932), but has not become popular.

Tetrachloroethylene and **carbon tetrachloride** are considered with the anthelmintics; see Index.

Dichloroethylene (*acetylene dichloride*), $CHCl.CHCl$, is also used industrially as a cleansing agent. Exposure to the vapor produces nausea and vomiting, weakness, tremor, epigastric cramps. Dermatitis develops in skin exposed directly to the liquid. The blood sugar level is low, the white count high. There was no evidence of renal damage. Intravenous injection of calcium gluconate relieved the cramps and vomiting (Wirtschafter and Schwartz, 1939).

Ethylene dichloride (*dichloroethane,* Dutch Liquid), $CH_2Cl.CH_2Cl$, a colorless oily liquid, is used industrially as a solvent, particularly for rubber. Digestive derangements, drowsiness, tremor and nystagmus are reported from chronic exposure to its vapor (W. D. McNally and Fostvedt, 1941). It is one of the more toxic of the halogenated hydrocarbons. High concentrations in air produce narcosis and pulmonary congestion. Many animals develop hemorrhagic necroses in the adrenal cortex. Kidney and liver injury is less than with chloroform or carbon tetrachloride. Various chemical agents confer some protection, especially methionine and choline (Heppel *et al.,* 1946). Dogs and foxes, but no other animals tried, develop bilateral swelling and turbidity of the cornea with concentrations that had no other ill effects. It generally clears when exposure is discontinued (Heppel *et al.,* 1944).

1, 2-Dichloropropane (*Propylene Dichloride*), $CH_2Cl.CHCl.CH_3$, used as a solvent substitute for carbon tetrachloride, is one of the most toxic of the halogenated hydrocarbons. The liver injury is greater with low protein, choline-deficient diets, and some protection is furnished by dl methionine and by choline plus l cystine (L. A. Heppel, Highman and Porterfield, 1946).

Tetrachloroethane (acetylene tetrachloride), $CHCl_2—CHCl_2$, was employed in the airplane industry as a solvent for cellulose acetate, but has been displaced largely by less dangerous solvents. It is also used in dry cleaning. Its inhalation produces hepatic degeneration with symptoms analogous to those of phosphorus or chloroform poisoning (Alice Hamilton, 1917, bibliography). H. A. Coyer, 1944, reported seven cases, one fatal. They developed hepatic cirrhosis, hemorrhagic diathesis with bleeding into the intestinal tract, and frequently ascites.

Trichloroethanol resembles avertin in action, and has a wider margin of safety. It is more soluble and more stable in water. It is excreted in the urine, partly unchanged, partly conjugated as glycuronate (G. Lehmann and Knoefel, 1939).

Carbon disulfide, CS_2, resembles the chlorinated methanes in its effects. It is a volatile liquid (boiling at 46° C.) with highly explosive vapor, extensively used in the manufacture of viscose rayon, and in the rubber industry as solvent for sulfur chloride. It has about the same acute toxicity as chloroform and produces similar effects, including vomiting, weakness, convulsions and unconsciousness. Chronic poisoning is much more common and leads to nervous and mental disturbances, based on extensive anatomical changes in the peripheral nerves and in the ganglion cells of the cerebral cortex.

Chronic poisoning **is especially common in the viscose rayon industry. Susceptibility differs greatly, but most** workers exposed to the vapor present some deleterious symptoms, psychotic in about 3 per cent. They may not appear for several weeks and progress slowly. They begin with disturbed sensation (formication, headache, vertigo) and gastro-intestinal catarrh; then insomnia, fatigue, listlessness, loss of initiative, melancholia, erethismus, loss of memory, hysterical manifestations, exaggerated and then diminished libido and complete impotence (but chronic poisoning in guinea pigs did not result in functional or anatomic changes of the sex organs, male or female; Passerini, 1933). The symptoms usually disappear in a few weeks if exposure is discontinued. If it is not, polyneuritis develops, with tremors, muscular weakness, sometimes areas of anesthesia, and blindness from involvement of the optic nerve (Haas and Heim, 1911). Extension to the cerebrum results in encephalopathia, erethismus, apathy, hallucinations, mania, epileptic attacks. Ataxia has been reported. Marked marasmus develops. Death does not occur till late (F. J. Braceland, 1942; F. H. Lewey, 1941). Degenerative *histologic changes* are found in the blood (hemolysis, mononucleosis, anemia; no methemoglobin formation; H. Briegers, 1941), and in the nerve cells and dendrites, liver (vacuolization), kidneys and lungs. The fluid or vapor causes conjunctivitis and other local inflammatory changes in the eye; and *dermatitis,* with erythema, vesication, degenerative changes in the peripheral nerve endings, and even third degree burns on prolonged contact (J.A.M.A., *112:*2086). Poisoning in rubber works was described by A. L. D. Delpech, 1856; it is reviewed by A. Hamilton, 1915; Gordy and Trumper, 1938.

Dogs exposed to 400 ppm, eight hours daily for fifty-one days, developed similar symptoms and anatomic changes. Thiamine apparently conferred some protection (Alpers, Belett *et al.,* 1941).

Fate.—The solubility of carbon disulfide is so low that the tissues soon become saturated and no more can be absorbed, no matter how high the concentration inhaled, except as it is oxidized and excreted into the urine. About 85 to 90 per cent is oxidized to sulfate and organic sulfur compounds (R. W. McKee *et al.,* 1943). None is converted to hydrogen sulfide.

Enzymes.—The *succinic oxidase* system, which is important in nerve metabolism, is inhibited *in vitro,* but only with relatively large quantities of carbon disulfide. There is no inhibition of pyruvic oxidase or decarboxylase, nor of lactic dehydrogenase (McKee *et al.,* 1943).

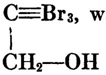
Fluorine Derivatives of Chloroform.—The substitution of F for Cl decreases the toxicity of chloroform progressively: Booth and Bixby, 1932, found the concentration of the vapors which kill guinea pigs in ten minutes as 7 per cent for $CHCl_3$, 21 per cent for $CHCl_2F$ and 63 per cent for $CHClF_2$; so that each F lowers the toxicity by a third.

The pharmacology of *saturated fluorocarbons,* with one to six carbon atoms, was studied by Struck and Plattner, 1939. They are irritant and narcotic.

Dichlorodifluoromethane, CF_2Cl_2, *"Freon,"* CCl_2F_2, boiling at −29° C., is the preferred refrigerant in refrigerating machines, and is used in "bombs" for spraying insecticides. Its toxicity is relatively low. Inhalation of 20 per cent vapor produces analgesia and confusion, but not unconsciousness. Tremors are prominent, and convulsions may occur with high concentrations (Brenner, 1937). Recovery is complete in ten minutes. Animals survive exposure to 20 per cent for 120 hours, and to 80 per cent for fifteen minutes, but not for thirty minutes. It is noninflammable, but in the presence of flame it may be partly decomposed, producing phosgene, chlorine and volatile acid.

Trichlorofluoromethane, $CFCl_3$, is also less toxic than chloroform. It boils at 24° C., while chloroform boils at 60° C.

TRIBROMOETHANOL; AVERTIN

Tribromoethanol,  $\begin{array}{l}\mathrm{C{\equiv}Br_3}\\ \mid\\ \mathrm{CH_2{-}OH}\end{array}$, was introduced under the name "aver'tin" as a fixed-dose anesthetic for rectal administration, to produce a somewhat evanescent surgical anesthesia. Its chemical structure is that of ethyl alcohol, with the substitution of three bromine atoms. This greatly intensifies the narcotic effect, analogous to the relation of chloroform to methane. It is improbable that the bromine plays a direct part in the narcosis. Tribromoethanol is soluble in water (1:30 at 40° C.), but solution occurs slowly, and aqueous solutions are prone to decompose, with formation of hydrobromic acid and dibromacetaldehyde, which is very irritant. It is therefore marketed as "Solution of Tribromoethanol" ("Avertin with Amylene hydrate;" formerly "avertin liquid"), a solution of the substance in amylene hydrate, corresponding to 1 Gm. of tribromoethanol and 0.5 Gm. of amylene hydrate in 1 cc. of the solution. The amylene hydrate renders avertin more rapidly soluble, but it also modifies the action, for it is itself narcotic, and increases the depth and especially the duration of the anesthesia, and adds to the respiratory depression. Tribromoethanol solution has attained considerable vogue for producing rather *deep basal anesthesia.* It is also used against tetanus and other convulsive conditions. The rather prompt recovery of consciousness is sometimes advantageous. In neurosurgery it is preferred because it lowers the intracranial pressure (which is generally raised in inhalation anesthesias). Full anesthesia is dangerous. Even the basal anesthesia should not be employed by those inexperienced in its use. The effects and the fatalities approach rather closely those of chloroform, except that hepatitis is not so common, perhaps because it is not used for prolonged anesthesia. Visceral diseases, infections and chronic alcoholism are cited as contraindications (Petermann, 1930).

Patients prefer tribromoethanol anesthesia; they drowse off promptly and awaken in about half an hour, with the whole ordeal over. There are practically no disagreeable sensations and no nausea, because the action passes off rapidly and completely. The *disadvantages* are inherent in fixed-dose anesthesias, which preclude control of the effect once the dose has been administered. The response of the patients varies considerably, owing in part to differences of the distribution of the enema in the colon. There may be some rectal irritation, but with proper use this is trivial. Respiratory depression is liable to complicate and prolong the induction of supplementary inhalation anesthesia. Some patients react with alarming early depression, usually transitory (H. K. Beecher, 1938). Postanesthetic sleep may be prolonged from six to thirty hours, or there may be prolonged delirium, requiring close surveillance. Patients often require catheterization. Avertin is not advisable for *obstetric amnesia,* since uterine atony results from doses above 50 mg. per Kg. (H. Killian, 1929). Special contraindications are numerous.

Historical.—Tribromoethanol was introduced by Willstaedter and Duisberg, 1923, 1926. Eichholtz, 1927, 1929, investigated its anesthetic action on animals and clinically. Its pharmacology was studied by Straub, 1928, and its clinical introduction promoted by Bützengeiger, 1927 (reviews, Council on Pharmacy and Chemistry, 1937, J.A.M.A., *109*:952).

Administration.—Tribromoethanol solution is administered exclusively by rectum, dissolved in warmed distilled water (not to exceed 40° C., to avoid decomposition), in the ratio of 2.5 cc. in 100 cc. of the dilution, so that each cubic centimeter contains 25 mg. of tribromoethanol and 12.5 mg. of amylene hydrate. It should be tested with congo red just before injection; acid solutions should be discarded. A cleansing enema is given on the preceding evening and another three hours before the operation. Half an hour before operation, the avertin solution is instilled into the rectum during five to seven minutes. It produces some local irritation followed by local anesthesia. Morphine, 10 mg., is often administered before the tribromoethanol, but is not necessary and it increases the risk of respiratory failure (Barlow and Duncan, 1933), as do also other sedatives.

Dosage.—The ordinary dose is 50 to 80 mg. of avertin (with 25 to 40 mg. of amylene hydrate) per Kg. of body weight. This quantity should not ordinarily be exceeded for basal anesthesia, although for young and vigorous subjects it may be increased up to 100 mg. of tribromoethanol (with 50 mg. of amylene hydrate). Serious toxic effects in the early clinical use were due chiefly to excessive doses and to ignorance of the contraindications, but even 100 mg. per Kg. occasionally causes complete anesthesia with circulatory and respiratory depression. The total dosage should not exceed 9 to 10 cc. of avertin with amylene hydrate for men, or 6 to 8 cc. for women, regardless of body weight.

Sequence Anesthesia.—The ordinary doses often fail to produce complete unconsciousness, and with half the patients they require to be supplemented by ether (Petermann, 1930) or N_2O. The effects of these are additive (ether, I. G. Karber and Lendle, 1929; nitrous oxide, rats, O. W. Barlow, Duncan and Gledhill, 1931).

Contraindications (relative or absolute, depending on the condition of the patient) include liver or kidney dysfunction, severe cardiac disease, old age, shock or dehydration, sepsis, toxemia, severe pulmonary tuberculosis, empyema, marked hypothyroidism, obesity, asthenia, cachexia, ileus, tumors of the colon, enteritis and acidosis (N.N.R.). Acute renal insufficiency is an absolute contraindication, as it increases the toxicity by interfering with the elimination. *Hyperthyroidism* (or thyroxin administration sufficiently in advance) is said to hasten the destruction and therefore to decrease the efficacy of tribromoethanol.

Administration in Tetanus.—The spasticity and convulsions may be controlled within ten minutes by 25 to 50 mg. per Kg., supplemented by 10 to 15 mg. per Kg. every fifteen to thirty minutes as needed. A light narcosis should be continued for two or three weeks, until convalescence is definitely established (R. Spaeth, 1940). Tetanus antitoxin should be administered in the meantime.

The course of the narcosis is rapid and brief after rectal administration of the ordinary doses. They reach their maximum in ten to twenty minutes, are distinctly decreased by forty to forty-five minutes, and consciousness has returned completely in sixty to ninety minutes after the injection. With larger doses, this is followed by prolonged sleep (H. Killian, 1929). In rabbits and rats, full consciousness is usually restored in thirty to fifty minutes after a full narcotic dose. Good *analgesia* in the sense of indifference to pain is obtained, as with chloroform, when the patient is partially conscious and able to appreciate sensations (clinically, M. Rodecurt, 1929; rats, O. W. Barlow, Duncan and Gledhill, 1931). Muscular relaxation is also good. Postanesthetic nausea is less than with ether.

Postoperative Events.—Shortly after regaining consciousness, the patients generally fall into a quiet sleep, lasting several hours (sometimes even for a day), from which they can, however, be readily roused. Continuous vigilance is necessary to maintain an open airway and to prevent cyanosis and respiratory failure. Postoperative excitement and delirium are not common, and generally yield to morphine. There is often considerable amnesia of the events of the next twenty-four hours. Severe headache ensues exceptionally and persists for one to three days. Cough is present for two or three days in about 5 per cent of the patients.

Fatalities.—Tribromoethanol produces serious fall of blood pressure and depression of respiration which may be fatal. Early collapse, marked cyanosis and persistent unconsciousness indicate a bad prognosis. The therapeutic margin is narrower than with ether (L. Lendle, 1928). The danger is increased by the variability of absorption and excretion. The clinical mortality approaches that of chloroform (1:500 to 1:2000; Beecher, 1938). A large proportion of the recorded deaths (reviewed by F. Eichholz, 1930) occurred with doses of 75 to 100 mg. per Kg.

Treatment of Untoward Effects.—Barlow *et al.* found picrotoxin with ephedrine the most effective treatment, but they do not greatly decrease the mortality. Ephedrine, caffeine, cocaine, nicotine and carbon dioxide were practically ineffective. Ephedrine, however, interrupts or shortens the narcosis clinically and in animals (Raginsky and Bourne, 1931). Riedel, 1930, claimed that administration of sugar diminishes the toxicity.

The fatal dosage for animals is reported by Barlow *et al.*, 1931. Lendle, 1933, found that *young rats* are somewhat more tolerant than adults, both as to narcosis and fatality.

Individual Functions.—The *narcotic effects* are similar in animals and in man. Rabbits, *f. i.*, when injected rectally with 0.3 to 0.5 Gm. of avertin per Kg. show excitement and prompt narcosis (Herzberg, 1928). Rats are tranquillized so that they do not struggle when tied in the supine position, after injection with 47 per cent of the M.L.D. of avertin with amylene hydrate, as compared with 37.5 per cent of the M.L.D. of avertin crystals, and 78.5 per cent of amylene hydrate (Barlow and Gledhill, 1933).

Site of Narcotic Action.—H. Cushing, 1931, concluded that tribromoethanol depresses the diencephalon, for patients in tribromoethanol anesthesia fail to give the normal severe reaction to the injection of 1 to 1.5 cc. of pituitrin into the third ventricle. However, Chauchard and Monod, 1931, showed that the action extends also to the cortical centers.

The *respiratory center* is depressed in tribromoethanol anesthesia, even more than with chloroform. The ordinary clinical dosage causes marked respiratory slowing, diminished response to carbon dioxide, and sometimes fatal respiratory arrest (F. B. Parsons, 1929; Hoepfl, 1930). With rabbits, the respiration rate is decreased to a fourth by the dosage required for full anesthesia. The depression is enhanced by morphine (G. Karber and Lendle, 1929; H. Killian, 1930). In rats, respiratory depression occurred with 46 per cent of the minimal tranquillizing dose of avertin with amylene hydrate, with 25 per cent for avertin crystals, with 75 per cent for amylene hydrate. Morphine potentiated the respiratory depression more than the sedative action (Barlow and Gledhill, 1932).

Circulation.—Ordinary doses of tribromoethanol generally produce considerable *fall of blood pressure*, usually of short duration (maximum in eight minutes), and not directly dangerous (C. C. Greer, 1930; W. P. Kennedy 1930). This involves depression of the heart and of the vasomotor center; direct action on the blood vessels, similar to that of alcohol, and decrease of the blood volume approaching that of severe hemorrhage. The *heart* is depressed directly, both by tribromoethanol (H. Guggenheimer and Fischer, 1927) and by amylene hydrate (E. Harnack and Meyer, 1894). Clinically, however, there is little effect on the heart, even with doses considerably higher than those used in clinical anesthesia (Raginsky, Bourne and Bruger, 1931). Electrical changes are exceptional and slight (Morton, 1935). Much higher concentrations, in animals, slow the heart, diminish the output and increase the coronary flow. Tribromoethanol anesthesia sensitizes the heart to epinephrine irregularities. Avertin *lowers the intracranial and intra-ocular pressure*, during fifteen or twenty minutes. Gas and ether anesthesia increase these pressures (Seevers *et al.*, 1931; W. Bourne, 1934). While these and other anesthetics dilate the pial vessels in cats, tribromoethanol decreases their diameter (Finesinger and Cobb, 1935).

Gastro-intestinal motility is considerably depressed even by hypnotic doses of tribromoethanol, the stomach more than the ileum, and this more than the colon; but the effect passes off as the patient awakens (Quigley, Barlow and Himmelsbach, 1934).

Parturition.—The uterine contractions are slowed (Dodek).

The *urine output* is suppressed for two hours in nearly 75 per cent of the human clinical anesthesias, chiefly by the fall of blood pressure, and is still low after twenty-two hours. The urea output is likewise lowered. In dogs the urine secretion is suppressed for one or two hours by anesthetic doses (Bruger *et al.*, 1930), and large doses produce definite histologic lesions. Human kidneys appear more resistant, but albuminuria and hemorrhagic nephritis are seen occasionally. Acute renal disease materially slows the excretion of tribromoethanol, and its toxicity is correspondingly increased.

Metabolism.—The *temperature* falls; the *blood sugar* rises. The alkali reserve is lowered, the blood bicarbonate being diminished. The *acidosis* approaches that of chloroform, but is less marked in man than in dogs (M. Bruger *et al.*, 1930).

Liver.—Moderate doses appear to have little effect on the normal liver, no more than amytal or ether (P. Kaczander, 1930; Bruger *et al.*, 1930). Impaired liver function is reported in 1 or 2 per cent of clinical administrations. It is generally slight and transient, but ordinary doses may exceptionally produce severe hepatitis and nephrosis, similarly to chloroform (D. H. Andersen, 1945). Large doses or with liver disease produce toxic hepatitis in dogs (E. Heinecke, 1930; Bourne and Raginsky, 1931).

Rectal Irritation.—Tenesmus and bloody stools sufficient to be mentioned in the record occur in about 1 per cent of clinical anesthesias; about a fourth of these are fairly severe. They occur both without and with amylene hydrate. The latter is more irritant in dogs. It is advisable to flush the rectum after the anesthesia is no longer needed. The rectal inflammation, with various visceral lesions, is generally responsible for delayed fatalities in rabbits (A. H. Maloney, 1942).

Absorption, Fate and Excretion.—These explain the rapid course. With rectal injection of tribromoethanol, 50 per cent may be *absorbed* in ten minutes, 75 per cent in twenty-five minutes, and the remaining 25 per cent very slowly (A. Speigel, 1930). The absorption is rather variable, however. The addition of amylene hydrate increases the speed of absorption in dogs (Quigley, Barlow and Himmelsbach, 1934).

The *excretion* occurs by the urine, almost as rapidly as the absorption, so that the sojourn in the body is brief; 70 to 80 per cent may be excreted in twenty to thirty minutes, and 95 per cent in the first two hours (D. A. Wood, 1930). When renal function is impaired, the toxicity may be considerably increased (Veal, Phillips and Brooks, 1931). The greater part is *detoxicated by conjugation* with glycuronic acid before it is excreted (Endoh, 1924; Welsch, 1929). The bromine remains in the molecule and is not ordinarily excreted as ion (Straub, 1928), but a case of bromide rash has been reported. In rabbits, the *tissue concentration* of avertin decreases in the order: liver, heart, brain, kidneys, lungs, spleen, blood (Fischer and Hüppmann, 1934). The concentration in the blood reaches its maximum in twenty to thirty minutes after the rectal injection. Narcosis occurs with 6 to 10 mg. per 100 cc. of blood; awakening with 2 or 3 mg. (review, Anschütz, 1930). G. A. Emerson and Morrison, 1942, report on the Br distribution in cats receiving tribromoethanol, tribromoacetaldehyde (bromal) and tribromoacetic acid.

Amylene Hydrate, dimethylethylcarbinol, tertiary amyl alcohol, $(CH_3)_2C_2H_5COH$, contributes a little to the narcosis and somewhat more to the respiratory depression (Barlow and Duncan, 1932). It has been used as a hypnotic, ranking between chloral and paraldehyde, in doses of 1 to 2 Gm. Its maximal hypnotic dose for man is generally stated as 4 Gm.; this is the amount contained in 8 cc. of avertin with amylene hydrate, which is the ordinary therapeutic dose. The fatal dose for animals is about 1 or 2 Gm. per Kg. The pharmacology of amylene was studied by E. Harnack and Meyer, 1894.

Amylene Hydrate, U.S.P.; a clear, colorless, volatile liquid of aromatic odor and taste. It is soluble in 8 parts of water, and freely soluble in alcohol. It forms acicular crystals on cooling.

Derivatives.—The hypnotic and lethal doses of various trihalogenated alcohols and their derivatives were investigated for rats by Burtner and Lehmann, 1938. They report that *trichloroethanol* has a wider margin of safety than tribromoethanol (avertin).

Trialkylmethanols are all narcotic, but much less so than tribromoethanol (Rice, Glenn *et al.*, 1938).

PREPARATIONS.—***Solution of Tribromoethanol,** U.S.P.; **Avertin with Amylene Hydrate.** Bromethol. Each cubic centimeter of the fluid contains 1 Gm. of tribromoethanol and 0.5 Gm. of amylene hydrate.

Tribromoethanol, U.S.P., a white crystalline powder of slightly aromatic odor and taste. It is volatile and unstable in air, slightly soluble in water (about 1:35). It melts at 79° to 82° C. It contains 84.8 per cent of bromine. Average dose (also for avertin), rectal, 60 mg. per Kg. of body weight, the total not to exceed 8 Gm. for women, 10 Gm. for men, regardless of weight.

ALIPHATIC HYPNOTICS

Sleep is one of the earlier phenomena of light narcosis and may be induced by small doses of any of the aliphatic narcotics. With many of these, however, the hypnotic stage is too brief, passes too easily into general anesthesia, or is complicated by undesirable side actions, stimulation, local irritation, and so on. Clinical somnifacients may be conveniently grouped into those which induce sleep promptly, and those which maintain it; evipal and barbital illustrate the extremes.

Historical.—The somnifacient properties of alcohol and of opium were known and used in antiquity. The first addition to these was bromide, introduced by Laycock in 1853, as a sedative in epilepsy, but not used as hypnotic until 1864, by Behrend. Five years later (1869) Liebreich added chloral hydrate. This was twenty-three years after the discovery of ether anesthesia. There was again a gap of thirteen years, followed by the introduction of paraldehyde (Cervello, 1882), urethane (Schmiedeberg, 1885), and sulfonal (Baumann and Kast, 1888); another gap of fifteen years, then barbital (E. Fischer and Mering, 1903); another gap of nine years, then phenobarbital against epilepsy (1912). Since then other barbiturates have been introduced in large numbers which, because of their potency, relative safety and comparative freedom from untoward actions, have largely displaced the other hypnotic drugs.

Chemical Grouping.—The hypnotic hydrocarbons and their halogenated derivatives may be grouped under the principal headings: (1) Oxygen substituents of hydrocarbons— alcohols (avertin, isopral, amylene hydrate), aldehydes (paraldehyde, chloral), ketones (sulfonals), ethers and esters (urethane). (2) Ureides acyclic (carbromal) and cyclic (barbiturates, hydantoins) and tetrahydropyridines. The ethyl group and the next higher homologues seem to be especially valuable in conferring hypnotic action, and are most effective in the presence of aldehyde or ketone radicals. Alcohol radicals weaken the action, so that glycerin, *e. g.*, is not narcotic. The compounds must resist oxidation sufficiently to make their action lasting.

Role of Chlorine.—The narcotic effect is greatly enhanced by the introduction of chlorine, as shown by the comparison of acetaldehyde and chloral, and by the methane derivatives, the efficiency of which increases for each additional chlorine atom from methane to carbon tetrachloride. This peculiar property of the chlorine compounds has not been explained.

Actions.—Small doses of these drugs depress sensory and intellectual processes, so that the perception of external stimuli is lowered (Kraepelin, 1892). The subject is thus put into a condition favorable to natural sleep. This should be the aim in their therapeutic use. Larger doses produce an actual stupor and eventually coma.

Other functions behave as in natural sleep:

The blood pressure and pulse are somewhat lowered. The skin vessels are moderately dilated. The brain vessels are also dilated (Berezin, 1916). The visceral vessels are constricted. The secretion of sweat is increased; the urinary, lacrimal, salivary and gastric secretions are decreased, the movements of the empty stomach are increased (Carlson). The chlorinated hypnotics (chloral) in large doses have a direct depressant effect on the medullary centers, especially the respiration, and on the heart muscle. All the members are hemolytic when added directly to blood (L. Herrmann).

Relation to Sleep Centers.—The narcotic action of the hypnotic drugs may be conceived as protecting the sleeping center against awakening impulses. Since all kinds of somnifacient drugs induce sleep in animals whose hemispheres have been removed, indeed often more effectively than in normal animals (Morita, 1915; Esser, 1931), their action must be chiefly on the basal centers, but this does not exclude that part of their action may be cortical in intact animals. These remarks apply to all the hypnotic drugs, and a division into "*cortical* hypnotics" (alcohol, paraldehyde, morphine, bromides, urethane, magnesium) and "*basilar* hypnotics" (barbiturates and chloretone) does not appear sufficiently justified (review, M. Kochmann, 1936).

Older views conceived sleep purely as a passive process, somewhat as a profound degree of inattention to the external and internal impressions of consciousness. The rhythm of awakeness and sleep persists, however, in animals deprived of hemispheres and cerebellum. This would leave the brain stem, the region of the basal ganglia, the corpora striata and mammilaria and the optic thalamus as the focus of sleep regulation. This is confirmed by the observations that this is the seat of degenerative lesions in the persistent sleep of lethargic encephalitis, and experimentally, by the production of orderly sleep of apparently normal type, by electrical stimulation of the floor of the third ventricle in cats (Hess, 1932, 1933; Marinesco) or by injection of 4 or 5 mg. of calcium chloride into this region, in cats (A. V. Tonkikh, 1941). Transection of the brain stem behind the third cranial nerves also produces in cats a condition apparently identical with natural or barbital sleep, which persists indefinitely and includes extreme miosis and suppression of olfactory and ophthalmic reflexes (Bremer, 1935). All these experiments create artificial conditions, and it may therefore be questioned whether they are conclusive for ordinary sleep; but they are currently accepted and sleep is accordingly conceived as an active process provoked by stimulation of the "sleep centers" in the basal ganglia, which in turn blocks the access to them of the awakening impulses from the cerebral cortex (cerebral sleep); or (somatic sleep) from autonomic "awakening centers," situated somewhere more posteriorly, in the vicinity of the oculomotor center, whose electrical stimulation may awaken sleeping cats (Economo). Progressive transections of the brain stem in rats indicate that the caudal area of the hypothalamus is concerned with keeping awake, the preoptic area with sleep, perhaps by inhibiting the caudal area (Nauta, 1946).

The classification of cortical and basilar hypnotics was based chiefly on the ambiguous potentiation between the hypnotics (Molitor and Pick, 1926), and on the report of Keeser, 1929, that the concentration of the barbiturates is higher in the mesencephalon than in the brain generally. The distribution has been contradicted by Koppanyi and Dille, 1935, but it would not be very cogent since it would depend on the ratio of white and gray matter rather than on selective action. Gensler, 1915, found the concentration of hypnotics in the whole brain somewhat higher than in the other tissues, including the blood. A. E. Laidlaw and Kennard, 1940, report that India ink injections show numerous dilated capillaries in the hypothalamic nuclei with barbiturate anesthesia, but few with ether.

Direct injection of phenobarbital into various cerebral areas results in sleep from the infundibular regions, not from the telencephalon, rhinencephalon or cerebellum (Sahlgren, 1934). The effects of intracisternal injection of hypnotics were reported by Borbely, 1935 (animals); and Urban, 1935 (human) and by S. J. Weinberg, 1934.

Neurohistological degenerations after long-continued use of fairly large doses of barbiturates occur throughout the central nervous system, but especially in the cerebellum, midbrain and spinal cord (Mott, Woodhouse and Picksworth, 1926). It is improbable that these have any relation to the hypnotic action.

The *antagonism and synergism* of the various hypnotics with stimulants of the mesencephalon, such as tetrahydronaphthylamine (Morita, 1915), coramine and ephetonin (Moritsch, 1932), for normal and decorticated rabbits is complex and confusing. The "basilar" hypnotics render the cortex more susceptible to ether and other anesthetics, so that they probably also have a cortical action, especially with large doses.

Brain potentials have been studied especially with barbiturates. These result in the large regular alpha waves characteristic of normal sleep or cerebral transection, interpreted as disconnecting the cerebral cortex from the disturbing impulses of the awake state. However, barbiturates also render the cortex much more susceptible to the abolition of the waves by ether, indicating direct cortical depression; and anesthetic doses of barbiturates (or avertin) abolish the waves even without ether (Bremer, 1936; Berger, 1934; Derbyshire *et al.*, 1936).

Blood Lipids.—The influence of continued administration of aliphatic hypnotics was investigated by Waser, 1915.

Inflammation.—Chloral, urethane, and presumably the other aliphatic narcotics, inhibit the migration of leukocytes from the inflamed frog's mesentery (Ikeda, 1916).

Glucose Tolerance Test.—Clinical doses of chloral, barbital, pentobarbital and morphine lower and shorten the hyperglycemia (H. Tod, 1935).

Comparison of Aliphatic Hypnotics.—Chloral, the oldest member of the group, is a good somnifacient, but it has been largely displaced by the newer hypnotics, perhaps not quite deservedly. Its action is certain, prompt, but sufficiently lasting, and easily graduated by the dosage. It is readily soluble, and not cumulative. It has an unpleasant taste and is somewhat irritant to the stomach. It is not effective against pain. The large doses originally employed sometimes produce dangerous cardiac and respiratory depression. It is doubtful whether these effects need be feared with doses of 1 Gm., but it is generally advised to be cautious in its employment in the presence of depression of the medullary centers, or of vascular, cardiac, renal, pulmonary or gastric disease. *Paraldehyde* is milder than chloral, but acts promptly. It does not affect the respiration or heart, but as unpleasant to take. *Barbital* (veronal) is about as effective, but not quite so prompt, is chloral. It is less disagreeable to taste, and is not so toxic; but full doses have caused severe and fatal poisoning, and therapeutic doses may produce cumulative effects. *Phenobarbital* (luminal) is more active and more toxic than barbital, but small doses are merely calming and sedative, like bromides, so that it has found a special field in epilepsy and in thyroid disease. *Amytal* and especially *pentobarbital* induce sleep more promptly, but do not maintain it so long, and leave less of a mental fog. *Carbromal* (adalin) and *bromural* act rather feebly, and *like the bromides* are suitable mainly for mild nervous insomnias. *Sulfonal* and *trional* are fairly powerful, but act slowly and produce considerable after-depression; they also irritate the kidneys and cause dangerous cumulative effects.

The *relative clinical effectiveness of various somnifacients* may be estimated from the data of Grabfield, 1931, and expressed as the average dosage (in Gm.) required to assure a good night's sleep to hospital patients indiscriminately, as follows, in ascending order (the more important drugs are in italics): *Codeine,* 0.0175 (*Pentobarbital,* 0.046, assumed as one-half of amytal); neonal, 0.058; *phenobarbital,* 0.072; ipral, 0.085; *amytal,* 0.94; phanodorn, 0.11; *chloral,* 0.155; *barbital,* 0.16; chlorbutanol, 0.18; butylchloral, 0.21; sabromin, 0.32; bromural, 0.41; carbromal, 0.43.

Comparison with Other Groups.—Morphine is ordinarily less effective than chloral, but is superior when insomnia is due to pain. *Scopolamine* is used especially in psychic insomnia and insanity. *Apomorphine* is said to be superior in acute alcoholism. *Bromides* are effective only in mild nervous cases, worry, and the like.

Mixtures of Hypnotics.—Urethane and opiates give only simple summation of action in animals (Le Heux, 1919). The older work, which claimed potentiation, appears open to criticism (Storm van Leeuwen, 1919).

Experimental criteria of hypnotic action are difficult, as this is influenced greatly by external conditions, such as fatigue or freshness, quiet and excitement. The *depth of sleep* may be measured quantitatively by the rise of carbon dioxide tension in the alveolar air (Regelsberger, 1934). The daily activity may be recorded by automatic devices; *f. i.*, by suspending an aluminum cage from a spiral spring (Schlaginweit, 1928). Sedation may be tested against excitement induced by cocaine (for mice, 1 mg. per 100 Gm. of body weight, hypodermically; Modrakowski and Rusiecki, 1937); with rats, by the quieting of the struggles when the animal is kept tied in the supine position.

Therapeutic Indications.—Hypnotics are used to procure sleep in insomnia, especially when more physiologic measures (removal of the cause, and so forth) are not applicable, and to break incipient habits of insomnia, by promoting the confidence and equanimity of the patient. Their continued use generally leads to tolerance and often to dependence and addiction. They should be avoided if possible. Full doses often produce acute poisoning. Doses only large enough to induce sleep indirectly by quieting the patient are rarely dangerous, and can be used temporarily without apprehension. When the hypnotic needs to be continued for a long time, it is well to change occasionally to a hypnotic of another type, and to return to the first later.

The *consumption of hypnotic drugs* has attained astonishing proportions, especially since the introduction of the convenient and relatively safe barbiturates. Five million ounces of these were sold in the United States in 1940, equivalent to more than four million sleeping doses per day (Klumpp).

Toxicology.—Suicide by hypnotic drugs, especially the barbiturates, becomes increasingly frequent, especially in large cities, where barbiturates are the means of 2 to 17 per cent of all suicidal deaths from poisons (exclusive of carbon monoxide) (W. E. Hambourger, 1939). Some of the suicides are accidental, the whole supply of drug being consumed by "automatism" in the twilight zone induced by the first dose (Richards, 1934). The *symptoms* are similar for all hypnotic drugs, passing through deep sleep, stupor and coma, often lasting for several days. Death occurs from narcosis of the respiratory center or from low blood pressure and temperature fall, or subacutely from lung complications (deglutition pneumonia) or nephrosis. The renal damage is often much greater than the urine findings would suggest. Oliguria may be marked. Edema is not common. Glycosuria occurs with normal blood sugar level, so that it is renal. Liver injury, from slight jaundice to acute yellow atrophy, has been observed with chloral and with nirvanol. *Recovery symptoms* after severe poisoning are similar to those after anesthesia, but with a slower course. Fever is common. The *treatment* should begin with gastric lavage. Activated charcoal may be useful. Severe cases may be treated by full doses of picrotoxin or metrazol with ephedrine (see under Barbiturates). Lumbar puncture has been advocated to relieve the high cerebrospinal pressure.

Efficiency of Respiratory Stimulants against Poisoning by Aliphatic Hypnotics.—Metrazol and coramine are fairly effective in rabbits (O. Gros, 1936), but are improved by the addition of epinephrine (Barlow *et al.*). The quantitative differences of various analeptics were studied by Chakravarti, 1939.

Largest Doses from Which Recovery Has Been Reported Clinically.—Leschke gives these as 8 Gm. for hedonal; 15 Gm. for bromural, adalin (carbromal) and phanodorm; 16 Gm. for trional; 26 Gm. for amylene hydrate; 30 Gm. for sulfonal; 150 Gm. for paraldehyde. Further data will be found under the individual drugs.

Addiction to soporifics is not uncommon, in the sense of indefinitely continued use from dread of insomnia. Some individuals respond with euphoria or inebriation, and use the drugs for this purpose, often with increasing doses. They can be fairly easily withdrawn, without marked abstinence symptoms. The immediate dangers are similar to those of abuse of alcohol, doubtless including greater automobile accident hazard. Severe addiction may lead to mental deterioration, similar to progressive paresis, sometimes with a parkinsonian syndrome.

CHLORAL HYDRATE

Chloral hydrate, $CCl_3.CH(OH)_2$, is the hydrate of *trichloraldehyde*, $CCl_3.CHO$. It was discovered by Liebig in 1832, and was introduced as a hypnotic by Liebreich in 1869. Chloral forms analogous compounds with alcohol and glycerol, with quantitatively identical actions.

Therapeutic Uses.—Chloral is used especially in insomnia of psychic origin. In ordinary nervous insomnia it should be given in small doses of 0.3 to 1 Gm. (5 to 15 grains), sometimes with 1 Gm. of sodium bromide. It may be administered in milk or in Orange Syrup, but its taste is not easily disguised. Larger doses are needed in mania and in delirium tremens. In the latter condition, the large doses have caused collapse. It is not very effective against febrile delirium or pain. The addition of morphine is said to secure a stronger effect than if either were used alone (Knell, 1907). Chloral is effective against the *convulsions* of strychnine, tetanus (Dreyfus, 1914), eclampsia, and the like. Fairly large doses are needed, and it has been displaced by the barbiturates. Chloral is also used in *asthma* and *seasickness*, but the benefits are uncertain. Chloral *by rectum* is rather more effective than by mouth. It cannot be used hypodermically because of its irritant action. *Locally*, it is sometimes employed against neuralgia and pruritus, as an ointment (15 per cent) or as *chloral camphoratum*, N.F. (the liquid resulting by triturating equal parts of chloral and camphor).

Ordinary somnifacient doses, 1 or 2 Gm., produce drowsiness in ten or fifteen minutes, and quiet, sound sleep within an hour, mainly by diminishing attention to external stimuli. The sleep lasts at least several hours, but the patient can be easily and completely aroused, and awakens refreshed, generally without depressant after-effects. It does not easily create tolerance. Exceptionally, chloral produces excitement and even delirium. It is irritant and disagreeable to take and should perhaps be avoided in gastric and intestinal derangements. Emptying of the stomach is somewhat hastened by 0.6 Gm. of chloral, as also by sedative doses of amytal (Northup and Van Liere, 1946). A few patients develop lacrimation. The respiration and pulse are somewhat slowed and the blood pressure and temperature slightly lowered, but little more than in ordinary sleep (Alstead, 1936). In respiratory and especially in circulatory diseases, these depressant effects may be rather more pronounced, and may perhaps lead to some cyanosis with the larger doses. In fact, however, the fear of respiratory and cardiac depression is based essentially on faulty deductions from animal experiments. There is no good clinical evidence of cardiac depression; while the danger is greater in cardiac diseases, it has often been given without bad effects (Cushny, 1914). The experimental evidence also indicates that the depressant dose is considerably larger than the therapeutic hypnotic dose (Gunn, 1914).

Larger doses, 2 or 3 Gm., produce deep sleep, which, as the dosage is increased, passes into stupor and coma, with complete muscular relaxation. The other depressant effects become much more important. The depression of the medulla makes itself felt by *slowing of the respiration* and *fall of blood pressure*. The vasomotor paralysis is so prominent that chloral is used in the laboratory to secure paralysis of this center. The pulse is also slowed through direct depression of the cardiac muscle. *Dilatation of cutaneous vessels* is quite marked and causes fall of temperature with large doses, aided by diminished production of heat from muscular relaxation and depression of the heat-regulating centers. The temperature regulation in deep chloral coma resembles that of cold-blooded animals (Sollmann and Hatcher, 1908). *Skin eruptions* sometimes follow. Death is ordinarily caused by paralysis of the respiratory center, although it may take place by paralysis of a weakened heart.

The cardiac effects are similar to those of chloroform. They consist in shortening of the refractory period and depressed contractility. With *stimulated ventricular segments*, the shortening of the refractory state leads to superposition of contractions and tetanus, and because of the depression, the tetanic contraction may be lower than the normal single twitch. The threshold of stimulation is not materially raised (Sasaki, 1921). Applied to the *exposed heart* of frogs or turtles, chloral produces progressive slowing, diminished contractility, lessened systole, and diastolic standstill. The arrested heart at first responds easily to stimuli, but cannot be started by atropine (Razewski, 1870; Harnack and Witkowski, 1879). Further details are described by W. H. Schultz, 1906. The *excised* frog heart (Straub arrangement) shows marked lengthening of the refractory period (K. Gies, 1927). Similar depressant effects are seen in the *mammalian heart* (Bock, 1898; Gunn, 1915). The depressant concentration is at least 1:1000; the fatal, 1:400. The oxygen consumption of the heart is decreased, but not so much as its activity (Rohde and Ogawa, 1912). *Sudden stoppage of the heart* may occur from relatively small doses, in cats, under the influence of excitement (Sollmann, 1908). This resembles some of the human cases. The *accelerator mechanism* is generally depressed by chloral (Fredericq, 1913).

Excised Intestines.—The movements are increased by 0.05 per cent, and diminished by stronger concentrations. This may be preceded by stimulation. Later, there may be occasional slow but strong contractions (Sembdner, 1913).

The *urine flow* is diminished during the narcosis (Ginsberg, 1912), as is also the phenol-s.-phthalein output (Whipple and Speed, 1915). The uric acid excretion is somewhat increased (Abl, 1913). The output of nitrogen and neutral sulfur is increased; but in *distinction to chloroform*, this is delayed for several days after administration (Harnack and Remertz, 1893); nor is the disturbance so great as with chloroform. Doses so large as to maintain anesthesia over twenty-four hours may not produce the characteristic effects of prolonged chloroform administration on the *liver and kidneys*, or only occasionally and to a slight degree (Hopkins, 1912). Severe chloral coma, however, is followed by prolonged anorexia, marasmus and loss of weight (Sollmann and Hatcher, 1908). Lissauer, 1914, found changes in the cardiac ganglia in rabbits (which are specially susceptible).

The **local action of chloral** is sufficiently irritant to allow its use as a rubefacient. Its action on the stomach is consequently prominent; it must be largely diluted with water before administration, else it may produce vomiting. Large doses are liable to show after-effects, referable to a gastritis. Solutions of chloral hydrate are *antiseptic;* 5 per cent prevents putrefaction (Claude Bernard).

Acute Chloral Poisoning.—The lighter grades show the narcotic phenomena, together with gastric irritation and vomiting, sometimes followed by icterus and albuminuria, skin lesions and ataxia. In severe cases (as by "knockout drops") there is prompt collapse or delirium; pulse scarcely perceptible; severe fall of temperature; cyanosis; dyspnea or very slow respiration. In fatal cases, death is rarely delayed beyond five hours and may be almost immediate. Fatal relapses, after apparent recovery, have been reported (Purdy, 1889). Large doses may kill the fetus *in utero* (Jung, 1914). The *fatal dose* averages about 10 Gm., but varies greatly. Death has been reported after 1 to 3 Gm., and recovery after 10 to 28 Gm. (Lewin). Doses above 3 Gm. must be used cautiously. (The dosage for cats was studied by Sollmann and Hatcher, 1908.) The popular impression that the effects of chloral are potentiated by alcohol ("Mickey Finn" knock-out drops) is not borne out by animal experiments (W. L. Adams, 1943). The *treatment* of chloral poisoning consists in gastric lavage; emetics would often be ineffective. The patient should be kept warm. Metrazol and ephedrine are useful. Artificial respiration is given as needed. *Cerebral stimulants* are of little avail against toxic doses. Light chloral sleep, however, is easily broken by caffeine, cocaine or tetrahydronaphylamine (Airila, 1913).

Chronic chloral poisoning is not rare. It presents the symptoms and degenerations of chronic alcoholism, with more severe gastric and cutaneous manifestations. The tolerance is only moderately increased, and sudden death is not infrequent. Chloral habit is treated in the same general manner as other drug habits.

Habituation of animals to hypnotics occurs with chloral, amylene hydrate, paraldehyde and others of the fatty series, but not with urethane, bromural or sulfonal (Biberfeld, 1918). Chronic chloral poisoning was studied in dogs by Wallace, 1912. Habituation to morphine does not confer tolerance for chloral (H. B. Myers, 1917).

Growth.—Chronic chloral poisoning arrests the growth of young rats, which remain permanently stunted even after the chloral is discontinued (Sollmann, 1924).

Fate.—Chloral is readily absorbed from all mucous membranes. It is excreted by the urine, in one and one-half to eighteen hours as the nontoxic trichlorethyl-glycuronic acid (urochloralic or chloraluric acid) (v. Mering, 1881). This reduces Fehling's solution, and thus gave rise to the erroneous belief that chloral causes glycosuria. It polarizes to the left, but does not ferment. True hyperglycemia may occur in profound narcosis, analogous to chloroform (Jacobson, 1913). It is generally stated that trichlorethyl alcohol, $CCl_3.CH_2OH$, is formed as an intermediate product, but this is questionable, since the conjugation of the latter is slower (G. Lehmann, 1938).

A small part of the chloral is excreted unchanged; this is greater if the liver is injured, as by carbon tetrachloride (Mukerji and Ghose, 1941).Minimal traces, if any, are exexcreted as inorganic chlorides and chloroform.

Liebreich's Theory.—Liebreich, 1869, was led to try chloral by the assumption that it would be converted into chloroform in the organism, as it is by alkalis in the test tube. The theory was disproved: the blood and expired air contain no chloroform, or at most insignificant traces (Nicloux, 1906). Liebreich also stated that a fraction is excreted as chloride; this was contradicted by Kast, 1887.

Concentration in Blood and Tissues.—In light chloral anesthesia of dogs, the blood contains 30 to 50 mg. per 100 cc.; in deep anesthesia, 50 to 70 mg. With just fatal doses, the brain contains 57 to 58 mg. per 100 Gm. (Archangelski, 1901; Olszewski and Renescu, 1932).

***Chloral Hydrate,** U.S.P., Chloral; $CCl_3CH(OH)_2$. Colorless crystals, of aromatic odor and acrid taste. Slowly volatilized when exposed to air. Very sol. in water (1:0.25); freely sol. in alc. (1:1.3) or eth. and oils, fixed or volatile. *Incompatible* with alkalis, carbonates, antipyrine and alcoholic liquids containing between 10 and 50 per cent of alcohol (Hargreaves, 1932). Average dose, 0.06 Gm., 10 grains.

Bromal hydrate does not induce typical sleep, but causes coma and death, in doses much smaller than does chloral hydrate. It is also much more toxic to the heart and uterine muscle (Ken Ito, 1926).

OTHER CHLORINATED HYPNOTICS

Many of these have been suggested as substitutes for chloral, but they are not seriously superior. Several owe their activity to the liberation of chloral. Since promptness of action is generally desirable, the slow and uncertain liberation is a disadvantage.

Butyl-chloral Hydrate, Croton Chloral Hydrate, $CH_3.CHCl.CCl_2.CH(OH)_2$, was also introduced by Liebreich, 1871. Its action is more powerful but shorter than that of chloral (v. Mering, 1875). It has been used especially in facial neuralgia. Sol. in water (1:40); very sol. in alc. or glyc. Dose, 0.3 to 1.2 Gm., 5 to 20 grains. The *hypnotic trihalogen butyl alcohols* were investigated by Aldrich, 1916.

Chlorobutanol, U.S.P.; Chlorbutol, B.P.; acetone chloroform; *Chloretone*, $CCl_3.C(OH)CH_2CH_3$, occurs as a colorless crystalline powder, of odor and taste reminding of camphor; sparingly soluble in water (1:125); freely soluble in organic solvents. It acts similarly to chloral, and is probably rather more toxic (Impens, 1901); severe poisoning, but with recovery, is reported from 6 Gm. The therapeutic dosage is 0.3 to 1.2 Gm., 5 to 20 grains. The saturated solution (0.6 per cent) acts as a mild local anesthetic, antiseptic and preservative for hypodermic solutions. Chlorobutanol appears in the mother's milk after the continued administration of large doses, but not after therapeutic doses (Blanner, 1919).

Chlorobutanol is used as an *anesthetic for laboratory animals*, as it allows of long operations without requiring any attention. The dogs are given the usual dose of morphine. As soon as vomiting has occurred, 0.2 Gm. of chlorobutanol per kilogram of animal is administered by stomach tube or peritoneally (Rowe, 1916). The chlorobutanol is previously dissolved in the smallest possible amount of alcohol. The anesthesia is complete in fifteen to twenty minutes, and lasts several hours. The blood pressure falls rapidly in rabbits, slowly in dogs. In unanesthetized dogs it decreases the response of the respiratory center to carbon dioxide (Voegtlin and Wiggers, 1918). Chlorobutanol is inadvisable when it is wished to have the animal recover.

Excised intestines are depressed by chlorobutanol. This may lead to false results in testing epinephrine or pituitary solutions preserved by this drug (G. B. Roth; E. L. Blackman, 1922).

Chloralformamidum (Chloral Formam.) (*Chloralamid*), CCl_3.CH(OH).NH.COH, was introduced by v. Mering, 1889, with the idea that the formamide ($CHONH_2$) would counteract the medullary depression of the chloral. This was not realized; it is merely a less active hypnotic, being probably slowly decomposed into chloral. Sol. in water, freely in alc.

Chloralose, a compound of chloral and glucose, was introduced by Heffter, 1888 and 1893. It is often contaminated with the nonhypnotic but toxic parachloralose (Mosso, 1893). It is used chiefly in physiologic experimentation. Restricted doses paralyze motor and sensory spinal centers without interfering with reflexes (review, M. Kochmann, 1936). It reinforces epinephrine stimulation of the uterus and excised intestine; and decreases response to parasympathetic stimulation; for instance, vagus reflexes, or pilocarpine on intestine or uterus. The blood pressure falls, according to Hamet, 1928, and rises, according to Vincent and Thompson, 1928.

Isopral, trichlorisopropyl alcohol, is over twice as potent as chloral, and its action is prompter. Impens, 1903, claimed that it is safer than chloral, but Sollmann and Hatcher, 1908, showed this claim to be unjustified. Clinically, it is also uncertain and dangerous (Kleinschmidt, 1914).

PARALDEHYDE

Paraldehyde $(CH_3CHO)_3$, a polymer of acetaldehyde, was introduced by Cervello, 1882. Its actions are fundamentally similar to those of alcohol (Kraepelin, 1892), but the hypnotic effect is more powerful, and sets in promptly, so that the patient may be asleep in ten to fifteen minutes. The sleep is normal and, with ordinary doses, without aftereffects. The drug is less certain and less powerful than chloral, but therapeutic doses do not tend to depress the heart and respiration. Its principal disadvantages are the disagreeable pungent taste; fusel-oil odor of the breath, persisting over a day; irritation of the throat and stomach; dizziness and faintness. Tolerance is generally acquired (also by guinea pigs; E. B. Carmichael *et al.*, 1942) and addiction is not infrequent. This presents the phenomena of chronic alcoholism, including delirium tremens (Fornaca and Querelli, 1912; William Hartz, 1912).

Other Aldehydes.—Simple aldehydes are not narcotic, but become so by chlorination (chloral) and by polymerization (paraldehydes), provided that they are soluble in water. Of the polymeric aldehydes from formaldehyde to butylaldehyde, only the paracetaldehyde is practically suitable for narcosis; the others are too toxic, too insoluble, or not sufficiently hypnotic (Knoefel, 1933). Other aliphatic aldehydes are reported to produce arterial disease in rabbits (Denny and Frothingham, 1914). *Acetaldehdye* intravenously produces a pressor response similar to that from epinephrine. The action is peripheral, with marked potentiation by cocaine (E. E. Nelson, 1943).

Indications and Administration.—Paraldehyde is used to *secure sleep*, particularly in delirium tremens (Theunisan, 1915); in the insane; in alternation with other hypnotics. The ordinary dose is 3 cc., raised in severe cases to 5 to 15 cc. or, better, a teaspoonful every hour, until effective. It is best given in iced water, tea or claret. As it acts promptly, the patient should be in bed before the drug is administered. It should not be injected hypodermically, as it is quite irritant.

Slow intravenous injection of 1 cc. of undiluted paraldehyde is advised by I. S. Wechsler, 1940. It generally puts the patient to sleep immediately and stops the convulsions of status epilepticus. It may be repeated when the patient awakens. One would fear intravascular precipitation, but Wechsler states that he has not seen any ill effects.

Paraldehyde may be used for *basal anesthetic*, preparatory to ether, intravenously (0.15 to 0.2 cc. per Kg. of body weight, as 6 to 8 per cent in isotonic dextrose solution, injected in eight to ten minutes; Nitzescu and Iacobovici, 1934) or by rectum (0.5 cc. per Kg. as 10 per cent in normal saline; Foote, 1935; Whigman, 1935). It is reported to be highly effective for *obstetric amnesia*, without producing uterine inertia or fetal apnea, and with a minimum of restlessness. Its toxicity varies widely, however, and death has occurred occasionally from doses within this range.

In parturition, 30 cc. of paraldehyde in 60 cc. of olive oil may be administered by mouth or rectum. Its concentration in the blood reaches 11 to 33 mg. per 100 cc. Amnesia is incomplete below 20 mg. per cent; with the higher concentrations it is complete for about ten hours. The concentration in the fetal blood is about the same as in the mother's (H. L. Gardner *et al.*, 1940). H. F. Kane and Roth, 1936, advise a rectal technic, with a cleansing enema at the beginning of labor, followed by a saline enema, and this by the paraldehyde, 1.2 cc. per 10 pounds of body weight, mixed with 1.5 cc. of benzyl alcohol (regardless of body weight), and followed by 30 cc. of normal saline to diminish local irritation. Proctitis does not occur (H. F. Kane and Roth, 1936).

Metabolism.—Hypnotic doses (in dogs) lower the blood sugar, but have no effect on the nitrogen excretion. Anesthetic doses cause considerable hyperglycemia and glycosuria, and a decrease of nitrogen excretion (Powell, 1914).

The **acute toxicity** of paraldehyde is usually low, so that 100 Gm. generally produce only prolonged sleep; 150 Gm. have been survived, but the susceptibility varies, and the few recorded deaths occurred from moderate doses, 25, 52 and 31 Gm. or cc. by mouth (Kotz *et al.*, 1938), and 12 cc. by rectum (C. L. Burstein, 1943). Formation of large blisters has been reported. Anatomic and histologic lesions were described by P. Schneider, 1929. *The margin of safety* on intravenous injection is narrow in animals. *Autopsy lesions* consist in pulmonary congestion, edema and massive hemorrhage, and dilated right heart (C. L. Burstein, 1943).

Large doses of paraldehyde which lower the systemic blood pressure thereby also lower the cerebrospinal fluid pressure; smaller doses do not affect it (T. H. B. Bedford, 1946).

Fate.—From 70 to 88 per cent of the paraldehyde is destroyed. The destruction is materially decreased in hepatic insufficiency. The unoxidized fraction, 11 to 28 per cent, is excreted chiefly by the lungs; only 0.1 to 2.5 per cent by the urine (H. Levine *et al.*, 1940). *Acetaldehyde* is destroyed four times as rapidly as paraldehyde, and is not affected by liver injury (P. Hitchcock and Nelson, 1943).

Hepatic insufficiency causes a longer and higher blood-concentration curve of paraldehyde, presumably by slowing the destruction. The narcotic effect is therefore increased, although a given level of blood concentration produces the normal narcotic effect.

***Paraldehyde**, U.S.P. $(CH_3CHO)_3$, is a colorless transparent liquid, of strong characteristic odor and burning taste. Sol. in water (1:8), freely miscible with alc. Dose, 2 to 8 cc., ½ to 2 drachms.

ETHYLSULFONE HYPNOTICS

These were introduced by Baumann and Kast, 1888 Sulfonal has the formula $(CH_3)_2.C(SO_2.C_2H_5)_2$. Baumann and Kast believed that the hypnotic action is connected with the ethyl radicals, and is further enhanced by replacing the remaining methyl radicals with ethyl (*trional*, one replaced; *tetronal*, both replaced), but this has not been confirmed (Burger).

Sulfonal, Sulfonmethane, occurs as a white crystalline powder of bitter taste, slightly soluble in water (1:365), freely soluble in boiling water. It is a rather powerful hypnotic, but a weak analgetic. Its absorption and therefore its effects are slow, sleep occurring only after one to five hours, and its administration must be properly timed. The sleep lasts six to eight hours, and the effect persists somewhat during the next day, with vertigo, lassitude, drowsiness and depression. This is due to the delayed excretion, which is even slower than the absorption; thus it tends to cumulative effects and dangerous poisoning, if the administration is continued over longer periods. Sulfonal is therefore unsuitable for prolonged use. It does not induce tolerance, but may probably cause addiction.

The symptoms of *acute poisoning* consist in prolonged and profound sleep, with gradual failure of the circulation and respiration. Death occurs usually after several days. It has been reported from 5 to 30 Gm. (Knaggs, 1890); while 100 Gm. have been survived (Neisser, 1891).

Chronic poisoning has been produced even by ordinary therapeutic doses, when continued for some weeks. The symptoms develop slowly and consist in nervous depression, gastro-intestinal disturbances and urinary changes. The appearance of hematoporphyrin in the urine (dark cherry color) is particularly characteristic. Skin eruptions are sometimes seen. If the drug is stopped when the symptoms are light, recovery occurs, but is slow. After the urine changes have set in, the prognosis is discouraging; death occurs after some weeks by general exhaustion. The autopsy is generally negative. The occurrence of *hematoporphyrin* was described by Stokvis, 1889. It is rarely seen in acute poisoning, but is frequent and fairly early in chronic poisoning. It can be produced in rabbits, but not in dogs (Neubauer, 1900). Hematoporphyrin is also found in the bile (Pfoertner, 1914). With rabbits, hematoporphyrin appears in the urine after four to six days of daily administration of 0.375 Gm. of sulfonal per Kg of body weight. The greater part is excreted as a proporphyrin, which is converted into porphyrin by mineral acids (Laubender and Monden, 1938). There is no evidence of nephritis in rabbits (Polson, 1927).

Urticaria may be produced by local application to the scarified skin (Sollmann, 1917).

Excretion.—Sulfonal is excreted partly as ethylsulfonic acid, partly unchanged, by the urine and intestines.

Administration.—The ordinary doses, 0.75 to 1 Gm., 10 to 15 grains, or in severe cases 2 Gm., are taken in hot milk at least four hours before bedtime. A smaller dose may be taken the second night. The administration should not be continued beyond a week, when an intermission must be made. It is generally advisable to prescribe cathartics, alkalis and plenty of water.

Trional, Sulfonethylmethane, $(CH_3)(C_2H_5)C(SO_2C_2H_5)_2$, is more effective than sulfonal; being more soluble, its absorption and action are prompter, producing sleep in one-half to one hour. It has the same dangers as sulfonal, and the latter is more commonly used. A case of chronic trional poisoning is described by v. Noorden, 1916. Trional occurs as colorless, odorless, crystalline scales; bitter taste. Slightly sol. in water (1:200); sol. in alc. Dose, 0.3 to 1.2 Gm., 5 to 20 grains, as powder.

Tetronal.—Tetronal is less soluble, and therefore slow.

URETHANES

These are derived from urethane (ethyl carbamate), $H_2N.CO.OC_2H_5$. They have been disappointing clinically. The hypnotic action is feeble and patients soon become immune. The efficiency increases with the magnitude of the alkyl radicals (Binet). There is also a decided diuretic effect.

Urethane (Ethyl Carbamate) acts more satisfactorily on animals than on man, producing a rapid and profound narcosis, with little change in the circulation or respiration (Schmiedeberg, 1885). It is therefore employed as a laboratory anesthetic. The CO_2 threshold of the respiratory center is somewhat raised (Wieland, 1915). It decreases the oxygen consumption (Winterstein, 1914). Large doses cause in rabbits a vacuolar degeneration of the hepatic epithelium (Sollmann) and severe damage to the portal veins and sinusoidal capillaries in rats (Doljanski and Rosin, 1944). In mice, repeated urethane anesthesias are often followed by *pulmonary adenomas* (Henshaw and Meyer, 1944). Intraperitoneal injection into rats (0.1 Gm. per 100 Gm.) arrests *mitosis* in the cornea at all stages, not merely in the metaphase as does colchicine. Most of these animals later develop adenomatous lung tumors (M. F. Guyer and Claus, 1947). In a strain of mice, weekly administration produced *anasarca* with glomerular lesions; this does not occur with other strains or in rabbits (T. B. Dunn and Larsen, 1946; A. Kirschbaum and Bell, 1947).

It also lowers the phenol-s.-phthalein output (Whipple and Speed, 1915). Large doses produce *hyperglycemia*, independent of the quantity of liver glycogen and epinephrine, and unaffected by pituitary. Bang, 1914, believed that it acts through pancreatic degeneration. It is excreted as urea.

The pendular movements of *excised intestines* of rabbits are weakened by 0.3 to 2 per cent urethane (Hecht, 1926).

Urethane inhibits the *oxygen uptake* of mammalian tissue, but accelerates it in yeast. The permeability of the *capillaries* is increased (S. M. Landis, 1927). Application to the scarified skin produces a *wheal* (Sollmann, 1917) and dilatation of the capillaries and arterioles (Carrier, 1922).

Urethane, U.S.P. (Ethyl Carbamate), forms colorless, odorless crystals of saline taste. It is very sol. in water (1:0.5) and in alc. (1:0.8). Dose, 1 to 4 Gm., 15 to 60 grains. It is used to *increase the solubility of certain substances*, for instance, quinine hydrochloride.

Hedonal, methyl-propyl-carbinol-urethane, is twice as active as urethane (Dreser, 1899). It has the same general effects, its absorption is relatively slow and it is more toxic. Its dose is about double that of chloral. It has been used intravenously for anesthesia (Page, 1912); a 0.75 per cent solution in normal saline is injected at the rate of 100 cc. per five minutes, reduced to 50 cc. when anesthesia is attained. Its use is dangerous.

Alkoxyethyl Carbamates were reported as to narcotic potency by G. A. Emerson and Abreu, 1938.

CARBAMIDES

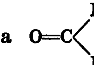
These are acylic ureides, with one H of the urea ($H_2N.CO.NH_2$) replaced by an acid radical to give a simple acyl urea, usually with a Br in the acid residue. The principal representatives are carbromal and bromural. They are rather feeble hypnotics and sedatives. Their therapeutic field is similar to that of the bromides, except that they are not used in epilepsy.

Carbromal (Bromdiethylacetylurea, Uradal, Adalin), $C(C_2H_5)_2Br.CONH.CONH_2$.—A white crystalline odorless powder. Very slightly sol. in water (1:3000); sol. in alc. (1:18). It is administered in powder or tablets. The sedative dosage is 0.3 to 0.6 Gm., 5 to 10 grains, three or four times daily; the hypnotic dose is 0.6 to 1.3 Gm., 10 to 20 grains. It is used against nervous insomnia. Poisoning by 15 Gm. was reported by Kirschberg, 1919.

Bromural, monobrom-isovalerianyl-urea, is a prompt but mild hypnotic, effective only in slight nervous insomnias. It is not analgetic, and is rendered ineffective by cough or delirium (v. d. Eeckhout, 1907; Sollmann and Hatcher, 1908). In man, 0.3 to 0.9 Gm. is effective in five to twenty-five minutes, producing a natural sleep lasting three to five hours, without excitement (Krieger and v. d. Velden). It dissolves in hot water, but not in cold.

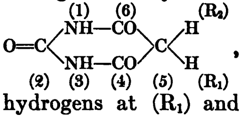
Sedormid is allyl-isopropyl-acetyl-carbamide. In hypersensitive patients theraputic doses may cause *thrombocytopenic purpura* and temporary inhibition of the maturation of the megakaryocytes in the bone marrow, probably by acting on some platelet-regulating center (S. Moeschlin, 1942; A. M. Hoffmann, Kahn and Fitzgibbon, 1938; McGovern and Wright, 1939).

BARBITURATES

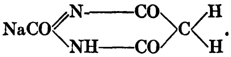
These have largely displaced the older hypnotics and sedatives, as they are effective and ordinarily without serious side actions. They are derivable from urea 

$$O{=}C\langle^{NH_2}_{NH_2}$$

, through malonylurea or barbituric acid



, by replacing both hydrogens at (R_1) and (R_2) with alkyl or aryl groups. Numberless derivatives of this pattern are easily produced, differing chiefly in potency and in rapidity of action. Many of these have been placed on the market since the introduction of diethyl barbituric acid ("veronal," barbital) by Emil Fischer and von Mering, 1903 (review, A. L. Tatum, 1939). Replacement of the CO of the urea by CS leads to a parallel series of hypnotics, the *thiobarbiturates*. Replacement of NH at (1) by CH gives the *pyridine* type of hypnotics, represented by *navigan*. The *hydantoins*, which are used in epilepsy, drop the CO at (6).

Barbituric acid and its substitute derivatives act as weak acids and form soluble salts of alkaline reaction, probably by trans-position into a lactim,  The "acids" are only sparingly soluble in water, but may be dissolved by conversion into the salts, or by addition of diethylamine or urethane. The salts form unstable solutions, decomposing gradually or rapidly with formation of ammonia and other products. Boiling hydrolyzes the solution with precipitation of the free acid, so that sterile solutions can only be prepared by sterilizing the dry acid before solution.

Constitution and Action.—The numerous barbiturates have in general the same actions, and in a therapeutic sense may be considered as different preparations of one substance. They differ in dosage, in duration of action, and somewhat in the breadth of the therapeutic zone (fatal dose: therapeutic dose). The relation of the substituted groups to the degree of pharmacologic action appears complex, as they are determined not only by the solubility coefficient and surface tension, but by the decomposition in the body.

Tatum, 1939, lists the following relations: (*a*) To be effective, both H atoms at (R_1) and (R_2) must be replaced by an alkyl or aryl group. (*b*) Increasing the length of the chains up to five or six carbons increases the potency. (*c*) Branched chains are likely to give briefer action than straight. (*d*) Unsaturated short chains are generally briefer than saturated chains. (*e*) Alkyl groups in ($_1$) and ($_3$) shorten depression and may produce stimulation. (*f*) Replacement of oxygen in ($_2$) by sulfur increases instability and shortens the action. Cyclic groups tend to render the compound inert, and benzyl groups make it convulsive. Tetra-alkyl barbituric acids have brief actions (M. T. Bush and Butler, 1937).

Duration of action is practically the most significant distinction of the barbiturates. The more important compounds (with their substituted groups) may be classified in order of decreasing duration (Gruber, 1941) as:

Long:

Phenobarbital = ethyl-phenyl
Barbital = ethyl-ethyl

Intermediate:

Neonal = ethyl-n-butyl
Dial = allyl-allyl
Ipral = ethyl-isopropyl
Alurate = allyl-isopropyl
Nostal = β-bromallyl-isopropyl
Amytal = ethyl-isoamyl
Sandoptal = allyl-isobutyl

Short:

Pentobarbital = ethyl-1-methylbutyl
Phanodorn = ethyl-cyclohexenyl
Ortal = ethyl-n-hexyl

Ultrashort:

Seconal = allyl-1-methylbutyl
Evipal = methyl-cyclohexenyl
Thiopental (Pentothal) = ethyl-1-methyl-butyl-2 thio.

A posological table for animals is furnished by Tatum, 1939.

Fate.—The excretion of the barbiturates occurs practically exclusively by the urine; the feces contain only traces. In the urine they occur partly unchanged (microscopic identification, O. Ehrismann and Joachimoglu, 1928), partly more or less split (J. Halberkann and Reiche, 1927), or conjugated with sulfuric acid or metabolized to urea (Stakol and Cerecedo, 1933). A part may disappear completely, probably by oxidation. The fate varies materially for the various derivatives, and these differences are chiefly responsible for the varying duration of the action (M. Reinert, 1928) which determines the therapeutic scope of these drugs; differences in the speed of absorption also play a part (Fitch, 1931). The shortest acting barbiturates are generally easily oxidized (Weese, 1936). Thiobarbiturates are destroyed rapidly.

Destruction in the Body.—Barbital and phenobarbital are the only barbiturates that appear consistently in the urine with ordinary therapeutic doses; the others only if the dosage is heavy (Herwick, 1931; Shonle, Keltsch *et al.*, 1933).

The site of detoxication, as judged by duration after excision of kidneys, or partial excision of liver (Masson and Belano, 1944), is chiefly in the *kidneys* with barbital; in the *liver* with amytal, evipal, ipral, pentobarbital, seconal, and most of the others; about *equally in liver and kidneys*, with dial, neonal and phanodorn; *chiefly in other tissues* with thiobarbiturates. Injury of the *liver*, for instance by chloroform, prolongs the action of the brief duration barbiturates (Pratt, 1933). *Ascorbic acid deficiency* impairs the production of enzymes connected with the destruction of the pentobarbital series, but not of barbital or of the thiobarbiturates (Kueter *et al.*, 1941; R. K. Richards *et al.*, 1941).

The "*biuret reaction*," under conditions which exclude confusion with others, is given by all barbiturates, but not by their decomposition products. It is a convenient qualitative and quantitative test if conditions are modified to exclude confusion with other biuret-reacting substances. Such tests are described by Herwick, 1934; Koppanyi, Murphy *et al.*, 1934; Brundage and Gruber, 1936. The urine must be examined promptly, as barbituric acid decomposes markedly on standing twenty-four hours (Ashe and Agricola, 1935).

Quantitative Urinary Excretion of Barbital (di-ethyl barbituric acid).—Clinically, 70 to 90 per cent can be recovered from the urine within a week (Koppanyi *et al.*, 1934); but the excretion is slow: for instance, 8 per cent in twelve hours, 20 per cent in a day, 36 per cent in two days; and traces are present for nine days (F. Reiche, 1926; Reinert, 1928). This slow excretion may give rise to cumulative action. The percentage excretion is not altered by habituation. The excretion is more prolonged with continued administration; a single dose of 0.3 Gm. required three days for elimination, but seven days were required after the same dosage had been continued daily for seven days. *Nephritic* patients require longer, six to eleven days; nephrosis, however, only the normal time (Arakawa, 1935; Argy *et al.*, 1936). In rabbits, the excretion is delayed by glomerular, but not by tubular, poisons, indicating that the excretion occurs in the glomeruli (Arakawa, 1935). With dogs, the normal excretion (74 to 82 per cent in seven to eight days) is increased by *theobromine* to 90 to 95 per cent in five days (Frostig and Engelberg, 1933). The rate and extent of its excretion vary in different kinds of animals: Rabbits excrete only half, dogs and cats relatively more (Koppanyi, Dille and Krop, 1934).

Excretion of barbiturate into breast milk can be demonstrated, but the quantity is generally too small to affect the nursling (Tyson *et al.*, 1938).

Placental Transmission with Soporific Doses.—Traces of barbiturate may be demonstrated in the amniotic fluid, placenta and fetus of rabbits receiving sodium barbital (Dille, 1936).

The *distribution in the body* was studied by G. Coronedi, 1928, for different compounds, as also their absorption and excretion. Data on the organ content in clinical poisoning and in rabbits are given by M. A. Jazzi-Mancini, 1923. Koppanyi, Murphy and Krop, 1934, found the barbiturate content highest in the liver, skeletal muscle and kidneys. The brain concentration was not high. The concentration in the blood corpuscles was a third that of the plasma. Kozelka, Tatum and Nelson, 1938, report that the ratio shifts with time. Ehrismann, 1928, reported on the concentration of barbiturates and ureid hypnotics in various *parts of the brain* by a sublimation method.

Therapeutic Uses.—The sedative action of the barbiturates is used to secure sleep, to dull worry and apprehension, and to calm nervousness and obtain tranquillity and rest in conditions ranging from "overwrought nerves" through drug addictions, hyperthyroidism, mania, chorea and epilepsy; the narcotic action is used to produce partial or complete unconsciousness in anesthesia, amnesia in parturition; and a hypnotic state suitable for psychiatric analysis. The effects can be readily graded in intensity by dosage, and in duration by the selection of the appropriate barbiturate. The barbituric acids may be administered by mouth as capsules; the sodium salts may be dispensed as capsules or powders, and dissolved in hot water, milk or a little tea. Administration by hypodermic and intravenous injection is especially important in obstreperous and maniacal patients (see, for instance, Blackwenn, 1930). With some patients considerable excitement precedes the sedative effect. Man is two or three times more susceptible than animals to the barbiturates, but there are marked individual variations to the identical dose, depending upon the nervous state: sensory and motor excitement require larger doses than depressed states (S. Weiss, 1929).

Advantages of the Barbiturates.—The effect is prompt, securing dreamless sleep in twenty to thirty minutes after oral administration, and immediately with intravenous injection. Even full anesthetic dosage produces little if any disturbance of other functions; the respiration, circulation, metabolism and the smooth muscles remain quite or practically normal until the fatal dosage is approached. There is no serious local irritation, so that the drugs may be administered by all channels, by mouth or rectum, hypodermically or by vein. There is no dangerous cumulation, and practically no habituation, no need for increase of dosage, and relatively small liability of addiction, beyond that entailed by the desire for easy sleep. The *disadvantages* are that the response is rather variable, markedly so in some individuals. The hypnotic effect is often preceded by considerable excitement, inebriation and even delirium; and the sleep and hebetude may be undesirably prolonged. Collapse occurs exceptionally. Severe cholera-like diarrhea has been reported. In some individuals, the barbiturates produce marked *skin reactions*, resembling urticaria, purpura, measles or scarlatina (Luce and Feigl, 1918). Moderate therapeutic doses of phenobarbital may aggravate the rigidity of parkinsonian conditions and are therefore contraindicated in this complex (Ziskind and Ziskind, 1937).

The *location of the central depression* is in the cerebral cortex and probably also in the subcortical ganglia (E. and J. Keeser, 1927), especially the hypothalamic portion of the diencephalon. Electroencephalogram effects of intravenous injection are described by Brazier and Finesinger, 1945. The bulbo-spinal reflexes are little affected (Pearcy and Weaver, 1927).

Use as Somnifacient.—The hypnotic dosage of barbital or phenobarbital, or their sodium salt, at bedtime, generally insures a natural, dreamless sleep, beginning in twenty to thirty minutes and lasting six to eight hours. The patient awakens refreshed, but may not be so alert as usual, and some lassitude persists during the day. With the other barbiturates, the duration of the sleep and of the after-inertia is shorter. Most subjects soon learn to compensate against the depression. Sodium barbital and phenobarbital are adequate for most somnifacient indications. With pentobarbital, the total action lasts only three to six hours, which is often too brief. The ordinary *hypnotic dosage*, taken half an hour to an hour before sleep is desired, is: barbital, 0.5 Gm.; phenobarbital, 0.03 Gm.; dial, 0.1 to 0.3 Gm.; ipral, 0.12 to 0.25 Gm; neonal, 0.05 to 0.1 Gm.; phanodorn, 0.1 to 0.3 Gm.; amytal, 0.1 to 0.3 Gm.; pentobarbital, 0.1 to 0.2 Gm.

Analgetic Action.—Ordinary hypnotic doses are analgetic to a rather limited degree. They have no effect on sensations other than pain (Wikler *et al.*, 1945). In normal men, the sensory irritability to faradic stimulation appears somewhat depressed (Hale and Grabfield, 1923). Clinically, satisfactory relief has been reported in severe burns, and in syphilitic gastric crises, by pentobarbital, 0.5 to 0.8 Gm. (Lundy, 1929). Migraine and other paroxysmal and recurrent *headaches* respond fairly well to phenobarbital, 0.03 to 0.045 Gm., three times daily; it may be necessary to continue the medication over long periods (Harris, 1922). In the treatment of headaches, and neuralgic and neuritic pain, the barbiturates are often prescribed together with the antipyretic analgetics. *Mixtures with aminopyrine* have been exploited under coined names, "veramon" or "peralga" with barbital; "allonal" with allyl-isopropyl barbituric acid. Their use has diminished greatly since it became recognized that they were the most frequent source of fatal aminopyrine neutropenia. Sedative doses of any barbiturate, or indeed any other hypnotic, may be prescribed extemporaneously, with analgetic doses of any antipyretic analgetic, including salicylates, acetophenetidin, and the like. Although objective clinical experiments are difficult to devise, it may be presumed that the tranquilizing effect of the hypnotics renders the patient more amenable to the analgetic action of the antipyretics, so as to constitute a kind of potentiation. Experiments on animals indicate summation of the narcotic, sedative, hypnotic as well as analgetic effects, and antagonism of the acute toxicity; *i. e.*, of the convulsant action of the antipyretics by the sedative action of the hypnotics. The details are complex, and the transfer of the animal data to the clinic is problematical (Kaer and Loewe, 1928; Starkenstein, 1925).

Use as Sedative.—This field is similar to that of the bromides, but the barbiturates act much more promptly, are less subject to untoward actions, and may be pushed to more profound effects. Skin eruptions occur only in especially susceptible individuals. In temperamental excitability or in emotional stress, barbiturates should be avoided, for fear of habituation. Sudden withdrawal of sedation sometimes leads to convulsions. They are useful in *toxic goiters* to lower the nervous excitability, the muscular activity and the basal metabolism; they allay the apprehension, and reduce the risk of operation (Rowley, 1921). They delay, more than ether, shock from exposure and manipulation of the intestines, but not hemorrhage shock (H. K. Beecher *et al.*, 1942). The barbiturates have been used successfully against the nervous *vomiting of pregnancy*, especially phenobarbital, 0.06 to 0.12 Gm., an hour before each meal and at bedtime, or hypodermically every four hours (Linkart, 1923; Miller, 1924). *Infantile pylorospasm*, pyloric stenosis and severe colic have been treated successfully with 0.008 to 0.015 Gm. of phenobarbital, crushed and given before or with each cereal feeding (Barnett, 1930). The usual *sedative doses* of the barbiturates are as follows, repeated at intervals of four to six hours, if needed: barbital, 0.1 to 0.15 Gm.; phenobarbital, 0.015 to 0.1 Gm.; amytal or pentobarbital, 0.02 to 0.04 Gm. Larger doses may be used if the patient is under close medical supervision; for instance, sodium amytal, to 0.2 Gm. every six hours or 0.4 Gm. every twelve hours. Barbiturates of brief duration are less suitable for sedation.

Considerably larger doses may be needed in *maniacal conditions*, in delirium tremens and in morphine withdrawal: phenobarbital, 0.6 Gm.; amytal, 0.4 to 0.8 Gm.; pentobarbital, 0.25 to 0.5 Gm. There may be some risk in repeating the larger doses within twenty-four hours. Sodium amytal or pentobarbital may be administered intravenously in these doses to delirious or maniacal patients. This has the advantage that the dosage can be adjusted to the response (C. B. Wilbur, 1944). Prolonged deep narcosis by sodium amytal has been used successfully in combat neurosis (Erb and Bond, 1945). M. M. Harris *et al.*, 1939, report transient amelioration in most schizophrenic patients who are subsequently benefited by insulin, indicating some prognostic significance. Sodium amytal, 0.25 to 0.5 Gm. hypodermically or by vein, may be used to break down the refusal of food by schizophrenic and other psychiatric patients; they often eat spontaneously immediately after the injection (Foley and Rossignoli, 1937).

Use in Epilepsy.—Barbiturates diminish the number and severity of the attacks, especially of the motor type, and thus indirectly improve the mental and physical condition of the patient. The improvement persists only during the medication. Acute attacks are controlled more efficiently than chronic or mild seizures (Grinker, 1922): idiopathic and traumatic epilepsies are more amenable than the senile and syphilitic. The effects and the efficiency are about the same as with bromides or dilantin, but one may succeed when the other has become ineffective. Combined medication with phenobarbital and dilantin is far more effective than either alone (B. Cohen *et al.*, 1940). Bromide may be added to phenobarbital to reduce the dosage of both (I. A. Darling, 1923). The barbiturates have several advantages over bromide in that the improvement is more rapid, and the undesirable side actions are less; they avoid the progressive psychoses of bromide, and the acne, fetid breath and dietary restriction. *Phenobarbital*, the first barbiturate to be introduced for this purpose (by A. A. Friedlander, 1912, and by A. Hauptmann, 1912), appears to be more active than other hypnotics, although these are somewhat effective (van Wert, 1920). It is not subject to serious idiosyncrasies, and does not appear to produce mental deterioration, even when 0.2 to 0.3 Gm. has been taken daily for two years (Somerfeld-Ziskind and Ziskind, 1940). The antiepileptic effect is not caused by the hypnotic action, for it is obtained undiminished when the phenobarbital is given with sufficient amphetamine sulfate (5 to 20 mg. by mouth) to prevent the hebetude and drowsiness (B. Cohen and Myerson, 1938; L. J. Robinson, 1941). The initial dosage of phenobarbital is 0.1 to 0.15 Gm. at night; increased by an additional dose in the afternoon and morning, if necessary, until increase of the dose does not further improve the condition. This averages about 0.2 Gm. (3 grains) per day, but ranges from 0.065 to 0.5 Gm. per day. Up to 0.7 Gm. (11 grains) per day may safely be taken over prolonged periods. It does not produce tolerance or addiction in epileptic patients. Severe attacks may be controlled immediately by intravenous injection of sodium phenobarbital (B. Cohen, Showstack and Myerson, 1940; L. J. Robinson and Osgood, 1940; W. G. Lennox, 1940).

Anticonvulsant Action.—The barbiturates may be used clinically as well as experimentally to suppress most if not all varieties of convulsions of central origin: traumatic tetanus (R. Spaeth, 1940), strychnine poisoning, meningitis, chorea, status epilepticus, tetany, eclampsia, cocaine poisoning, insulin overdosage. They are effective against convulsions induced experimentally from all central locations, the cerebrum, medulla or spinal cord (E. E. Stranson, 1932). They are highly successful against strychnine convulsions, good against metrazol, picrotoxin and coramine. They are also successful against cocaine convulsions. Their efficiency in developed cocaine poisoning depends on whether this takes the form of convulsions or of collapse.

Phenobarbital may be used prophylactically before local anesthesia, especially in hypersensitive subjects. Pentobarbital is the most potent of the commonly used convulsant antidotes; but amytal, avertin and chloral are also effective (Barlow *et al.*). The *anticonvulsant dosage* for pentobarbital is 0.25 to 0.5 Gm.; amytal, 0.4 to 0.8 Gm.; pernoston, 2 to 6 cc. of 10 per cent solution. The administration should be by slow intravenous injection. Relaxation and hypnosis occur in forty-five to ninety seconds. In the persistent convulsive states the dosage is repeated, by mouth, when the action wears off. Patients should not be kept continuously unconscious for more than twenty-four hours; if a longer action is necessary, the patient should be allowed to recover consciousness between the convulsions. In chorea and tetany the administration is as with epilepsy.

The antagonism of barbiturates against *acute cocaine poisoning* and other local anesthetic drugs was shown on dogs and monkeys by Tatum and Collins, 1925. Sulfonal and trional are also effective (Mendola, 1927). Not only are the convulsions suppressed, but the respiratory depression is decreased, and the minimal fatal dose is materially increased. Similar observations have been made on man (Guttman, 1926).

Antagonism to Insulin Convulsions.—Although the barbiturates have little effect on the insulin hypoglycemia, they suppress insulin convulsions and raise the fatal dose materially (I. H. Page, 1923; E. L. Jackson, 1931). Insulin or epinephrine administration before evipal *prolongs the sleep*, as compared with control mice (J. F. Reinhard, 1945).

Efficacy against Electric Convulsions in Cats.—Convulsions produced by the passage of an alternating current through the brain form a convenient means of testing the efficacy of anticonvulsants. Sodium bromide, 2 Gm., a dosage sufficient to prevent the cat from walking, raised the convulsant threshold by only one-half. Phenobarbital, 0.1 Gm., a dosage producing similar symptoms, raised the threshold to three or four times the normal. Comparable doses of other barbiturates had little anticonvulsant action. The highest ratio of anticonvulsant: hypnotic potency occurred with diphenylhydantoin, acetophenone and benzophenone (Putnam and Merritt, 1937). The *chronaxia of the nervous centers* is increased by barbiturates, decreased by strychnine, with mutual antagonism (Chauchard, 1934).

Barbiturates in Anesthesia.—Since the central effects of the barbiturates do not differ in principle from those of other aliphatic narcotics, they may be used alone, or in combination, to secure general anesthesia (Fredet and Perlis, 1924); or as premedication to anesthesia (Brumm, 1927); or for obstetric amnesia (Drabkin *et al.*, 1929). The chief difference from ether lies in their nonvolatility; they cannot, of course, be administered by inhalation; only by mouth, rectum, hypodermically, or by vein. The nonvolatility also precludes their excretion by the lungs and entails a more prolonged and continuous action. This secures steadiness of anesthesia, but restricts flexibility if the effect is too profound, as may easily happen, since the individual response varies considerably. This is especially serious, as deep barbiturate narcosis suppresses the response of the respiratory center to carbon dioxide so completely that breathing is continued only by the much less sensitive stimulation of anoxemia (E. K. Marshall and Rosenfeld, 1936; Y. Henderson, 1940). Safety can only be insured by doses which require to be supplemented by volatile anesthetics; or by adjusting the rate of intravenous injection to the effect, which is difficult since the full effect does not occur immediately. The duration of the postanesthetic stupor is also a serious objection to full anesthesia by barbiturates except for those of ultra brief action. *Barbiturates in conjunction with inhalation anesthesia* are a definite accession to anesthetic technic. They may be administered simply to assure sleep on the night preceding the operation; to tranquilize the patient, to remove nervousness and apprehension, and to secure smoother induction; or finally, to take a share in the anesthesia itself.

Laboratory Anesthesia.—Barbiturate anesthesia is used increasingly in laboratory technic, often supplemented by morphine and ether to maintain more constant conditions than is practical with inhalation anesthesia. As compared with other fixed dose anesthetics, they cause less disturbance of the circulation and respiration, of the reflexes, of the gastro-intestinal tract and of the blood sugar level; the recovery is much better. The duration of the coma is from three to five hours for pentobarbital and pernoston; twenty-four to thirty-six hours for barbital (Barlow, 1930). The barbiturates were originally administered by stomach tube, but they are now ordinarily given hypodermically or intraperitoneally (M. G. Mulinos, 1928) or, best, intravenously (Page and Coryllos, 1927). Rectal injection of pentobarbital is the most successful method of anesthetizing *chimpanzees* (J. H. Elder, 1937).

Preliminary Tranquilization.—In this field the barbiturates compete with morphine, and their action may be graded through a much wider scale, but perferably so that the patient is actually in a normal sleep when the inhalation is started. In emergencies, such as painful accidents or cesarean section, this sleep may be secured immediately by intravenous injection. In *local anesthesia*, the barbiturates have the additional advantage of being prophylactic against cocaine or procaine convulsions. Pentobarbital sodium, 0.2 Gm., 3 grains, by mouth, one and one-half to two and one-half hours before lumbar puncture, diminishes the pain and promotes the cooperation of the patient (S. H. Epstein and Marvin, 1932). Morphine is often added to enhance the sedative action, before and during the operation, diminishing the after-pain, and lessening the tendency to excitement during recovery from the anesthetic. It materially prolongs the depressant action (Lundy, 1930). It is inadvisable to use morphine with pernoston, because the additional depression of respiration may become dangerous.

Qualitative changes in the pernoston actions occur in mice if other drugs are added: with morphine, a characteristic posture of the hind legs develops, with abduction of the thigh and extreme flexion of the knee and hip; with benzedrine (as little as 0.05 mg.) there are fits of convulsive jumping; with coramine or metrazol, seminal ejaculation occurs (S. Loewe, 1938).

For basal anesthesia, with dosages that give the barbiturates a more or less equal share in the anesthesia, they diminish correspondingly the amount of the inhalation agent, and therefore diminish the undesirable side actions. The induction is tranquil, even more so than after morphine; the blood pressure, heart and respiration remain more nearly normal than with any other anesthesia (except for the tendency to respiratory depression with pernoston). Nitrous oxide is potentiated, so that surgical anesthesia may be maintained with an 80:20 mixture, allowing sufficient oxygen to prevent anoxia and to secure adequate relaxation. The reduction in the ether helps to prevent vomiting and postanesthetic nausea. The long sleep and amnesia after the operation ease the ordeal for the patient; those who have been subjected to several anesthesias generally prefer the barbiturate and nitrous oxide or ether sequence. The chief disadvantage of barbiturates consists in the varying susceptibility to the depression, particularly in occasional excitement; and in the duration of the postanesthetic stupor. When this is not too prolonged, it may be a positive advantage by resting the patient, as with pentobarbital, but it limits the use of barbital and phenobarbital; amytal and pernoston are intermediate.

Choice of Preparations.—This involves chiefly the duration of the effects; toxicity, *i. e.*, the margin between the therapeutic and fatal dose; and the personal experience of the physician with the drug. This last is an important element, and it is better to intensify one's experience by confining it to the agents which offer substantial advantages. Of these, the duration of action is clinically more important than the margin of safety, since the differences in the latter are not sufficiently large to appear practically important.

The experimental and clinical data as to the *duration of narcosis* vary considerably for want of a sharp end point, especially when comparing the results of different investigators. The dosage is an important factor. Fitch and Tatum, 1932, used 60 per cent of that dose which was fatal to 50 per cent of the animals. J. Pinkhof, 1930, employed a more complicated procedure, involving chiefly the time when half of the original dose must be injected to reproduce the original depth of anesthesia (a light narcosis). The *temperature of the room* has considerable effect on the response of mice (Raventos, 1938); these also show some seasonal variations of susceptibility to the somnifacient action and in the duration of anesthesia, but not in the toxicity (De Beer *et al.*, 1939). *Repetition* of dial anesthesia in dogs shortened the duration of the narcosis from eight hours to one hour; with phenobarbital anesthesia, repetition had little effect on the duration (G. H. Ettinger, 1938).

Procedure for Basal Anesthesia.—The administration of the barbiturate is begun on the evening preceding the operation, to insure rest. If pentobarbital sodium is chosen, this is given in capsules, 0.1 Gm. (1½ grains). A second dose of 0.1 to 0.2 Gm. (1½ to 3 grains) is given two hours before the operation, and repeated an hour before the operation. If sodium amytal is used, these doses are doubled. The last dose is generally accompanied by 10 mg. (⅙ grain) of morphine, and 0.4 mg. (1/150 grain) of atropine, hypodermically (Barlow, Fife and Hodgkins, 1934). The amount of the barbiturate should not produce deep narcosis, to avoid respiratory depression, especially if ether is used to complete the anesthesia (Lundy, 1932). The morphine dosage should be somewhat less than if barbiturate were not given; and barbiturates should not be used after large doses of morphine.

Effects of the Preanesthetic Dosage.—In the series of Barlow, Fife and Hodgins, 1934, about a fourth of the patients were asleep on arrival at the *operating room;* most of the others were drowsy; a few were inebriated, but were quickly calmed by nitrous oxide analgesia. The respiration was generally unchanged in rate, slightly reduced in depth, as by sleep. The pulse rate and blood pressure were generally practically unchanged. About a fifth of the patients had some conjunctival congestion, resembling that produced by alcohol, lasting about an hour. The *induction of surgical anesthesia with nitrous oxide:oxygen* was completed in three to six minutes. It was easily established and maintained, with a wider margin of safety. Respiratory depression occurred only if the dosage of pentobarbital exceeded 0.4 Gm. on the operative days. The *postoperative sleep* varied widely in duration, from a few minutes to ten hours, depending largely on personal factors and on the nature and duration of the anesthesia. The patient should lie on his side during the sleep, to prevent obstruction of the airway by the tongue. After the return of consciousness, the patient remains drowsy and sleeps much for a day or two; after amytal, there may be amnesia during this period (Zerfas and McCallum, 1929). *Postoperative restlessness and excitement,* tossing and incoherent talking, occurred in nearly a third of the patients, depending chiefly on their personality. It is generally inverse to the duration of the postoperative sleep, and can usually be controlled by small doses of morphine. *Nausea and vomiting* depend entirely on the supplementary anesthetic; they do not occur with local anesthesia. The *urine output* is decreased proportional to the water intake. Albumin is present in less than 4 per cent. Casts are rare.

Obstetric Amnesia.—This aims to induce a condition in which the patient is not actually unconscious, but is tranquilized and drowsy, so that she drops to sleep between pains, and the pains, although of undiminished force, are but little felt and not remembered. Morphine may be omitted or reduced to half. The uterine contractions are not weakened, even by fairly large doses (Dodek, 1932), and the better cooperation tends actually to shorten labor. The circulation, respiration and temperature remain normal, the babies are not notably narcotized and breathe promptly (Robbins *et al.*, 1925; Galloway *et al.*, 1936). However, some patients develop marked restlessness, and constant supervision of both mother and baby is essential. C. O. McCormick, 1932, reported that pentobarbital produces less delirium, greater amnesia and less protracted sleep than does amytal.

J. M. Dille, 1934, found the concentration of *barbiturate in the fetus* considerably higher than that of the mother's blood, uterus, placenta and amniotic fluid. Y. Henderson, 1937, warns that the dosage should be adjusted so that the barbiturate action has virtually ended before the third stage of labor is reached, since it would interfere with the carbon-dioxide response which normally initiates the respiration of the infant. Complete anesthesia of pregnant cats with pentobarbital profoundly narcotizes the fetus, so that most of these die within two hours. In rabbits, it appeared rather to increase the resistance of the newborn to asphyxia (F. F. Snyder, 1946).

Dosage for Obstetric Amnesia.—Pentobarbital sodium, 0.1 to 0.2 Gm. (1½ to 3 grains), or double this amount of sodium amytal, is administered when the patient is definitely in labor, with regular pains and beginning dilatation of the cervix. These doses may be repeated at intervals as needed, but the total should not exceed 0.5 Gm. (7½ grains) of pentobarbital or 1 Gm. of amytal (except against eclamptic convulsions). Barbiturates may also be used with scopolamine (O. S. Krebs *et al.*, 1936; P. P. Volpitto, 1946) and with the Gwathmey rectal anesthesia mixtures.

Barbiturate Narco-Diagnosis.—The inebriation grade of narcosis facilitates psychic control and renders the patient responsive to questioning, analogous to the "hypnotic state." This is utilized in the analysis of psychoses and in the treatment of schizophrenic patients. The brief-acting barbiturates are best suited to this purpose (Tatum, 1939; J. S. Horsley, 1943; Oxford University Press).

The inception and development of narco-diagnosis is sketched by H. K. Beecher, 1947; its present status is discussed by P. H. Hoch, 1946.

Thiopental (pentothal) sodium is most widely used, injecting 0.25 Gm. slowly by vein (R. G. Grinker, 1944). W. L. Hart *et al.*, 1945, prefer sodium amytal as giving a longer period for questioning; they inject a solution of 1 Gm. in 30 cc. of water at the rate of 0.06 Gm. or less per minute. At the end of the interview they inject 0.5 Gm. of caffeine-sodium benzoate hypodermically to facilitate return of awareness. Narco-analysis may also be practiced with *nitrous oxide inhalation* (C. H. Rogerson, 1944) and with *scopolamine;* but the greater tendency of the latter to produce delirium makes it undesirable.

Surgical anesthesia by intravenous barbiturates is convenient for brief operations, but is subject to serious risks. The pentothal death rate in the U. S. Army was about 1:5500. It is not suitable for office practice. It calls for special experience, rigid technic, and preparedness to deal with respiratory depression and oxygen: carbon dioxide imbalance, to which it is especially liable. It should be confined to the barbiturates with ultrashort duration: evipal, seconal and pentothal, preferably the last because it is briefest (R. C. Adams, 1944).

Intravenous barbiturate anesthesia is particularly dangerous in morphine overdosage, shock, liver damage, myocardial degeneration and in operations that interfere with the airway; it is not satisfactory for most abdominal operations or where highly excitable reflexes are involved.

Thiopental (Pentothal) Intravenous Dosage.—An injection of 4 to 6 cc. of fresh 2.5 per cent thiopental sodium solution (corresponding to 0.1 to 0.15 Gm.) is made in ten to fifteen seconds. This generally puts the patient to sleep. The injection is stopped for thirty to thirty-five seconds to permit the development of the full effect, and is then resumed at the rate of 4 to 8 cc. in one to three minutes, to a total of 14 to 25 cc. (0.35 to 0.625 Gm.), before starting the surgery. Relaxation need not be complete. The respiration is shallow, abdominal, with slight to moderate cyanosis. It is advisable to administer oxygen throughout the operation. Thiopental is rapidly destroyed in the body, so that it may be repeated as needed. Half of the usual dosage suffices for patients in shock, with or without hemorrhage (H. B. C. Sandiford, 1944). Debilitated and toxemic patients have a lowered tolerance.

Parenteral administration of barbiturates should be confined to direct anesthesia and pressing emergenices. Otherwise, oral administration should always be chosen, for safety, although the slower absorption entails the disadvantages of greater variability of response and longer duration of excitement.

Rectal and hypodermic injections are not often used, since the alkaline solutions are irritant. With intramuscular administration of the more potent barbiturates, the local irritation is usually slight (because of the smaller dosage), and there is less risk than with intravenous injection. The intramuscular dosage of sodium amytal is 0.1 to 0.5 Gm. (1½ to 7½ grains), as 10 per cent solution, and not more than 5 cc. should be injected at one site. *Intraperitoneal injection* is used in animal experiments, but necrotic ulcers may result if the injection should lodge in the walls of the stomach or intestines (Kistler, 1933).

Intravenous injection offers the tempting advantage of immediate effect and better control of immediate dosage. This, however, holds only for the more rapidly acting barbiturates. With barbital or pentobarbital there is an unexplained delay, up to twenty minutes, until the action is fully developed (T. Koppanyi, 1945; Kepmesch, 1933), so that there is danger of underestimating the eventual depression by the immediate response, and unless the injection is made slowly there may be an alarming fall of blood pressure to shock level, but usually of short duration. This is probably due to precipitation of the barbituric acids on contact of the strong solutions with the blood. It may be minimized by alkalizing the solutions with a buffer, but best by injecting slowly.

Sloughing may result if the strongly alkaline solution escapes into the subcutaneous tissue. In such an event, the site should be infiltrated with procaine hydrochloride solution (1 per cent in isotonic saline), which presumably acts as a buffer (Elder and Harrison, 1944).

Intravenous barbiturate anesthesia of experimental animals is convenient for avoiding abrupt changes in the anesthesia, with their disturbance of the circulation and respiration (C. J. Wiggers, 1942). Dogs receive a hypodermic injection of morphine sulfate, 3 mg. per Kg. In half an hour about two-thirds of the calculated anesthetic dose of the barbiturate (for barbital sodium, 175 mg. per Kg.) is injected into a leg vein during five minutes. The remainder is injected more and more slowly until the animal just fails to respond to cutaneous stimulation. The corneal and tendon reflexes are exaggerated.

Thiobarbiturates have the urea-oxygen of barbiturates replaced by sulfur. Their action is generally similar, but much shorter, since they undergo rapid *destruction* in the body, an hour being the maximum in dogs. They are more potent than the corresponding barbiturates, and larger doses cause injury of the liver, kidneys and brain (Gruhzit *et al.*, 1937); but these do not occur clinically (Tabern and Volwiler, 1935; Pratt, Tatum *et al.*, 1936; C. M. Gruber, 1937). Intravenous pentothal anesthesia has been discussed above.

Evipal, n-methyl cyclohexenylmethyl barbiturate of sodium (hexobarbital, evipan), was introduced especially for intravenous anesthesia, as its action is brief. It is destroyed in the liver, only 1.2 to 4.5 per cent appearing in the urine, in man. However, a number of deaths by depression of both respiration and circulation have been reported, and it must be used with discrimination. It may be employed with fair safety in a relatively narrow field, for analgesia, for induction and for brief anesthesia. It is generally aimed to produce merely inebriation, where mentality is confused and the consciousness of pain is lost. It has been employed especially in obstetrics (report of Council on Pharmacy and Chemistry, 1937, J.A.M.A., *108*). Consciousness returns in fifteen to thirty minutes, with the usual *dosage* of 2 to 4 cc. of fresh 10 per cent solution, injected at the rate of 1 cc. per ten seconds. It is dangerous to exceed a total of 10 cc.

Pharmacologic data for a variety of animals were reported by W. P. Kennedy, 1934. The dosage for full anesthesia is about 30 mg. per Kg. for cats, 35 mg. per Kg. for dogs. The M.F.D. is 100 to 110 mg. per Kg. The blood pressure generally falls, regardless of the rate of injection or the reaction of the solution. The fall is explained partly by peripheral vasodilatation, partly by cardiac depression (S. C. Daas, 1941). The hypnotic action is materially potentiated by acetylsalicylic acid, aminopyrine, demerol and morphine (Barlow *et al.*, 1942). The narcosis is prolonged by epinephrine, but not by insulin (J. F. Reinhard, 1945). Dallemagne claimed production of *profound anemia* in dogs, but Beecher, 1938, found no blood changes even when a dog was anesthetized twenty-two times with weekly intervals.

Seconal and sodium amytal are also administered intravenously, although their chief use is oral.

One gram of *seconal* intravenously in humans produces complete surgical anesthesia for one hour; the return to consciousness is complete in six to seven hours.

Sodium amytal is used as 10 per cent solution, freshly prepared within half an hour of its use from the anhydrous (not the ordinary) salt. This should not be injected faster than 1 cc. per minute. The single dose usually need not exceed 0.5 to 0.6 Gm. and should never be more than 1 Gm. The patient becomes drowsy when 0.1 to 0.2 Gm. has been injected. The speech becomes slurred, and at 0.35 Gm. sleep sets in, perhaps in the middle of a word. When the dosage exceeds 0.6 Gm., the anesthesia becomes profound: the pupils are contracted, fixed, sometimes irresponsive to light; the corneal reflex is diminished; the gagging reflex is usually present, the knee jerk exaggerated (Mason and Baker, 1930). With 0.65 to 1 Gm. of amytal the patient stays unconscious for one to six hours, sometimes longer, and then remains drowsy and sleeps at intervals, but cooperates in taking food and fluids. Restlessness may occur in the post-anesthetic period, and can generally be controlled by morphine.

The *pernoston* technic is exclusively intravenous. The maximal dose is set at 1 cc. of the 10 per cent aqueous solution per 12½ Kg. of body weight, *i. e.*, a total of 0.3 to 0.8 Gm. The injection is begun about fifteen minutes before the operation, and stopped as soon as the patient drops asleep, so that only a part of the dose may be required. The inhalation anesthetic is then administered. It is not advisable to give morphine with pernoston.

Side Actions of Barbiturates.—A considerable inconvenience of the barbiturates is the marked *variations of the central response* with different individuals, including delayed effects, extreme depression, excitement, even mania. These clear up eventually, but are seriously objectionable while they last (Bourne, 1934).

Relative Excitant Action of Various Barbiturates.—With trained dogs, Quigley, Barlow and Himmelsbach, 1934, found psychic excitement and restlessness more frequent with amytal than with barbital, and less frequent with pentobarbital than with either of the others. They also found it more frequent with small than with moderate doses. 5,5(1,3 *dimethyl-butyl*), *ethyl barbituric acid* is not depressant, but purely convulsant, resembling picrotoxin more than strychnine; its convulsions are suppressed by amytal (Swanson and Chen, 1939).

Respiration.—With oral administration, hypnotic doses produce slight slowing, chiefly through the sleep. Larger doses depress the respiratory center directly, reducing the depth and rate, often with irregularities (Page and Coryllos, 1926). The decreased oxygen saturation of the arterial blood after pentobarbital and amytal anesthesia may persist for four hours (Schnedorf, 1939). The respiratory depression is markedly accentuated by morphine and the supplementary inhalation anesthetics. With intravenous injection of clinical doses, the respiration becomes more shallow, and often slightly accelerated; but it remains regular (Zerfas and McCallum). Even hypnotic doses may paralyze the respiratory center, if they are injected too rapidly.

Intravenous injection of the short-acting barbiturates tends to produce adduction of the vocal chords, *increased laryngeal reflexes*, and coughing. It is attributed to central vagus stimulation. This may be temporarily relieved by epinephrine; atropine tends to prevent it (C. L. Burstein and Rovenstine, 1938).

Relative Respiratory Depression by Sedative Drugs.—Barlow and Gledhill, 1933, found that the tranquilizing dose of various sedatives required to quiet the struggling movements of dorsally bound rats, decreased the minute volume of respiration by the following average percentages: morphine, 30 to 45; pentobarbital, 40; avertin with amylene hydrate, 46; amytal, 70. Kleindorfer and Halsey, 1931, reported that dial and allurate cause markedly greater respiratory depression in cats than do amytal or avertin.

Respiratory Synergism with Morphine.—In rats the respiratory depression is but little greater (at most a third) than the simple summation of the effect of the morphine and of the amytal, pentobarbital or avertin. It is of about the same order of magnitude as the summation of their tranquilizing effects (Barlow and Gledhill, 1933).

Circulation.—Anesthetic doses cause no significant change in the circulation, clinically or in animals, with oral, hypodermic or slow intravenous administration. The blood pressure remains normal; the heart rate may be slightly quickened; the color of the skin is generally unchanged, sometimes pale or slightly cyanotic. Sedative doses significantly decrease the *loss of fluid* from burned tissue (Beecher and McCarrell, 1943).

Barbiturized animals are likely to respond to *vasomotor reflexes* (sciatic stimulation, Lacey, 1932; carbon dioxide inhalation, C. E. King, 1933) by fall of blood pressure, in contrast to the rise which these stimuli generally cause under other anesthesias, including chloral and avertin. The fall is partly vagal, partly vascular. On the other hand, barbiturates, especially amytal, decrease the response of the heart to *stimulation of the cardiac vagus* (Lieb and Mulinos, 1929; G. D. Shafer, Underwood and Gaynor, 1930). Acetylcholine and pilocarpine remain effective, suggesting that the action is on the vagus ganglia (Koppanyi, Linegar and Dille, 1935).

With rapid intravenous injection there is a prompt fall of blood pressure, averaging 30 mm. in clinical cases, generally with prompt recovery to the normal level. It is probably due to the temporary flocculation of the sparingly soluble barbituric acids, at the reaction of the blood; it may therefore be prevented by slow injection of dilute and alkalinized solutions (Zerfas and McCallum, 1929; Mason and Baker, 1930). Comparative studies on a series of barbiturates were made by Vogt, 1930.

With excessive doses, the pressure may remain low (Gruber and Basket, 1926), probably due to a direct action on the blood vessels, perhaps analogous to that of arsenic (Jacobi and Roemer, 1911; Jacobi, 1920). The spleen tends to become engorged so as to contain nearly a third of the red blood corpuscles (P. F. Hahn *et al.*, 1943). Peripheral vasodilatation can be demonstrated in dogs by the changes of the local temperature (Richter and Oughterson, 1932). This may also account for the *exanthemata*. *Urticaria* is produced by the local application of barbital to the scarified skin (Sollmann, 1917). *Perfused vessels* (cerebral) are dilated (Gruber and Roberts, 1926). Perfused frog legs are slightly constricted, and sensitized to epinephrine (O. Arnell, 1928). Dial lowers the susceptibility to ventricular fibrillation in response to galvanic stimulation (Rojas *et al.*, 1942). The *perfused rat heart* is depressed by the barbiturates (G. B. Roth, 1935). Relatively small doses increase the diastolic phase in heart-lung preparations (Olmsted and Ogden, 1930). Excised *frog heart* is depressed by all barbiturates, but with considerable differences of potency. The response of the *turtle heart* to vagus nerve stimulation is also depressed (C. M. Gruber and Keyser, 1946). The depression of perfused turtle heart is antagonized more effectively by theophylline than by coramine, metrazol, glycocoll or atropine (R. L. Johnston, 1938).

Smooth muscle is depressed by large doses, but in varying degree. Clinical doses do not produce significant effects; and even in full anesthesia, the depression is much less than with ether (Jackson, 1922; C. M. Gruber, 1925). The *uterus* is relatively resistant (Arnell, 1928). The parturient contractions are not affected by the full analgetic dosage (for instance, amytal, 0.018 Gm. per Kg. by vein, within two hours, Zerfas and McCallum, 1929; Drabkin *et al.*, 1929; Dodek, 1932). The uterine response to pituitary remains normal.

Ureteral contractions are depressed by anesthetic doses, and the contractor response of epinephrine is diminished (Gruber, 1928); but distention or pilocarpine produces peristalsis.

The motility of the *gastro-intestinal tract* is significantly reduced, and the emptying time of the stomach is markedly delayed (J. M. D. Olmsted and Giragossintz, 1929); an average of 20 per cent in normal man by 0.2 Gm. of sodium amytal (Van Liere and Northup, 1941); but adequate stimuli, such as distention or pilocarpine, evoke normal peristalsis.

With unanesthetized trained dogs, intravenous injections of barbiturates depress the motor activity of the stomach, ileum and colon. With equivalent anesthetic doses, the degree of the depressant action of amytal averages about $\frac{4}{10}$ that of barbital, and pentobarbital about $\frac{1}{4}$ of amytal. The gastro-intestinal depression is much shorter than the somnifacient action, but the different barbiturates range in the same order, pentobarbital lasting a third, and amytal two-thirds as long as barbital (Quigley *et al.*, 1934). The depressant effect occurs equally after decerebration, so that the action is peripheral (Quigley and Phelps, 1934). C. L. Burstein, 1939, claims that intravenous injection of clinical doses of barbiturates into dogs with Thiry-Vella fistula of the jejunum produces only a transitory depression, followed in five to fifteen minutes by increased tonus and motility lasting from ten minutes to two hours. *Excised* intestines of various animals are relaxed and depressed by the barbiturates; but thiobarbiturates produce a sequence of stimulation and depression (C. M. Gruber and Gruber, 1939). The *gastric and pancreatic secretion* of dogs are decreased by barbital (Barlow, 1927). Amytal also interferes with the response of the gastric and salivary secretion to parasympathetic stimulation (Macleod).

The *urine output* is not affected by hypnotic doses. It is generally decreased in basal anesthesia (Emge and Hoffmann, 1931). Anuria may occur with toxic doses. The suppression appears to be due to the lowered blood pressure and may be antagonized by epinephrine (H. Silvette, 1942). Increased excretion of *urates* has been reported for anesthetic dosages (Zerfas and McCallum, 1929). *Hematoporphyrin* occurs exceptionally in the urine of rabbits after barbital, but not after nostal or phanodorn (Laubender and Monden, 1938).

The **temperature** is lowered slightly by sedative doses, and markedly so in coma, owing partly to depression of the medullary centers, partly to diminution of movement. The fall is greater in animals, because of their relatively larger body surface (M. M. Ellis and Barlow, 1924; Deuel, Chambers and Milhorat, 1926; N. B. Eddy, 1929).

Basal metabolism is not significantly changed even by full hypnotic doses.

Deuel, Chambers and Milhorat, 1926, found no distinct change in patients, despite a fall of temperature of 2 or 3 degrees If shivering occurs, in animals, the basal metabolism increases. In the obstetric use of amytal, the maternal metabolism remains within the normal limits (Zerfas and McCallum, 1929; Robbins *et al.*, 1929). The variations reported for sedative doses of different barbitals in man, by Anderson, Chen and Leake, 1930, also appear within the normal range of variability.

Blood Sugar Level.—Contradictory results have been reported, depending partly on conditions, especially the diet. Anesthetic doses, according to most observers, cause no change in the blood sugar level of normal fasting animals (Dresbach and Randels, 1931; E. S. Jackson, 1931). A few have reported marked hyperglycemia (Soma Weiss, 1926; H. Jacoby, 1930). Olmsted and Giragossintz, 1931, who found no change in the sugar level of dogs when fed on meat, obtained hyperglycemia in dogs fed on a diet rich in carbohydrate. This is due to decreased rapidity of the assimilation of the circulating glucose, for injection of glucose produces greater hyperglycemia in barbital animals (Wierzuchowski and Gadomska, 1927). Amytal is said to prevent morphine hyperglycemia (Olmsted and Giragossintz, 1931). Barbital does not influence the effects of *insulin* on the blood sugar level, although it suppresses the insulin convulsions (E. L. Jackson, 1931). In the period *following barbiturate anesthesia*, the blood sugar falls, apparently by diminished hepatic glycogenolysis, diminishing the response to epinephrine. This effect is similar to that of chloroform and probably indicates incipient liver damage (Hrubetz and Blackberg, 1938).

Other Blood Constituents.—Bourne *et al.*, 1930, reported for dogs under amytal, concentration of the blood, decrease of *p*H, decreased blood alkali reserve and increased CO_2 combining power. Zerfas and McCallum, 1929, found no significant change in CO_2 binding power. The *coagulation time of the blood* is shortened in cats and pigeons (Ellis and Barlow, 1925). Ordinary doses had no significant effects on *liver function* in dogs (Bourne *et al.*, 1930). Toxic dosage produced changes indistinguishable from those of infectious diseases.

Serum choline esterase was lowered to a fourth by continuing barbiturate administration to patients for some weeks (F. Schultz, 1943).

Toxicology.—Barbiturates as a group are now the most common suicidal poisons, excepting carbon monoxide. In 1940, there were 545 barbiturate deaths reported in the United States (Klumpp). One-seventh of all cases of poisoning (exclusive of CO) treated in recent years in hospitals of the large cities of the United States were barbiturates. About 7.3 per cent of these proved fatal (Hambourger, 1940); but recovery may sometimes occur after four to six days of coma. Nearly all cases are suicidal, although not always intentional, additional doses being taken in the confused state induced by the therapeutic dosage. Some deaths are due to therapeutic overdosage. Hypersusceptibility is rare. The chief *phenomenon* of barbiturate poisoning is profound and prolonged coma (sometimes preceded by excitement); marked fall of blood pressure, depression and eventual paralysis of respiration.

The symptoms of barbiturate poisoning have been confused with those of uremia, epidemic encephalitis and opium poisoning. The reflexes are preserved, but greatly impaired. The muscle tonus is generally diminished; but with severe intoxication there may be parkinsonian katatonus (Meerloo, 1933) and tremors. Nystagmus is frequent, and diplopia has been reported. The pupils are generally dilated, but in severe poisoning they may be constricted and unequal (Roemer, 1919), until the final asphyxial dilatation. Skin eruptions are often associated with sharp febrile reactions, mucous membrane involvement and glandular swelling (Haubrich, 1934; Messinger, 1928). A few instances of fatal exfoliative dermatitis have been reported for phenobarbital (U. J. Wile and Benson, 1940; Sexton *et al.*, 1941). Some patients have marked jaundice. The temperature falls in the acute coma, but may then rise to a high fever. Such patients often develop bronchial pheumonia, sometimes even after the consciousness has improved (Chang and Tainter, 1936). Hypersusceptibility to therapeutic doses was charged for about 2 per cent of the toxic cases of Hambourger's series. Pneumonia after complete recovery from nostal is common in rats, and may occur with subnarcotic doses, in contrast to other barbiturates (Holck and Cannon, 1936).

Histologically, two fatal phenobarbital cases showed widespread degenerative changes in the central nervous system, and fatty degeneration in the liver, kidneys and capillaries (Jankovitch and Fazekas, 1932). Renal necrosis was reported by Rommel, 1912.

Clinical Fatal Dosage of Barbiturates.—The following tabulation of minimal dose reported as fatal (min.), and maximal dose reported as survived (max.), has been constructed from the data compiled by W. E. Hambourger, 1940, Pohlisch and Panse, 1934, and miscellaneous sources. No distinction is made between the free barbituric acids and their sodium salts. Highly questionable reports are omitted. *Allonal:* (min., 36 tablets; max., 40 tablets). *Alurate elixir:* max., six ounces. *Amytal:* min., 1.6 Gm.; max., 7 Gm. *Barbital:* min., 2 Gm.; median, 6 Gm.; max., 33 Gm. *Dial:* max., 2.4 Gm. *Phenobarbital:* min., 1.7 Gm.; max., 9 Gm. The wide margin for phenobarbital is probably a statistical accident. G. F. Kempf, 1946, concludes that death from oral administration of *barbital* or *phenobarbital* rarely results in adults unless the dose reached 6.5 to 10 Gm.; that 6 Gm. of amytal are not fatal unless complications develop; and that *pentobarbital* and *seconal* are not fatal with less than 3.25 Gm.

The LD_{50} *of oral administration to cats* is reported for several barbiturates by S. Krop and Gold, 1946.

Weight, Age and Sex on Barbiturate Toxicity in Animals.—Bazett and Erb, 1933, reported a logarithmic relation for pentobarbital with the *size* of dogs and cats, the per Kg. dose being smaller for large than for small animals. Most of the toxicity determinations have been made on albino rats, where the size becomes subordinate to the age and sex. Carmichael, 1937, found young rats (four weeks to nine months) more resistant than those more than nine months old; the M.F.D. of pentobarbital per Kg. with intraperitoneal injection was about a fifth higher for the young rats than for the older. For newborn rats, however, the M.F.D. per Kg. is only a third lower than for adults (Etsten *et al.*, 1943). As to sex, Holck reports that adult male rats are much more resistant than females to pentobarbital and to evipal. Different results were claimed by Moir and Waddell, 1938, for young rats. Nicholas and Barren, 1932, found gravid females twice as sensitive as males to amytal. Prolonged administration of testosterone to rats produces complicated changes in their susceptibility to barbiturates (H. G. O. Holck *et al.*, 1942). *Acute liver damage* by CCl_4 greatly increases the susceptibility of rats to the quickly acting barbiturates, pentobarbital and evipal, even before histological damage is present, probably by impairment of the detoxicating mechanism. This passes off quickly when the liver regenerates (Cameron and de Saram, 1939).

Alcohol is additive to barbiturate narcosis, materially increasing the toxicity (H. Ramsey and Haag, 1946).

The **treatment of barbiturate poisoning** is the same as for other hypnotic drugs. Gastric lavage is the first indication in recent oral cases. Emetics should not be used if the patient is comatose. The patient should be protected against overcooling. Artificial respiration should be administered if natural breathing fails. Deep barbiturate coma tends to poor pulmonary ventilation, atelectasis and eventually pulmonary edema, disposing to pneumonia. A free airway should be maintained, by frequently changing the patient's position and administering oxygen against anoxemia. Diuresis is best maintained by intravenous fluid. Prolonged coma lessens the chance of recovery, and if the patient is greatly depressed, and especially if the reflexes are absent, picrotoxin should be administered to improve the muscular tonus, reflexes, respiration and blood pressure, without aiming to restore full consciousness (D. L. Burdick and Rovenstine, 1946).

Picrotoxin, metrazol or coriamyrtin, in nearly convulsive doses, have a limited efficiency, mainly by stimulating the respiration, especially if used together with ephedrine (Maloney, 1931); but the dosage of the convulsants must be large to be effective, and somewhat excessive amounts increase the fatality. Artificial respiration alone may save from twice the fatal dose, and helps the other analeptics (Barlow, 1935). Nasal oxygen therapy is helpful (Schnedorf, 1939). Caffeine, camphor and carbon dioxide aid but little.

Amphetamine sulfate, intravenously, awakened patients who had received 0.5 Gm. of amytal, but some remained drowsy until a third injection of 10 mg. had been made, with fifteen minute intervals (Reifenstein and Davidoff, 1938). Freireich and Landsberg, 1946, recommend 10 to 40 mg. of amphetamine, as 1 per cent solution intravenously, followed every half hour by 10 to 20 mg. as needed. A total of 400 mg. appeared harmless.

Metrazol is fairly effective against the respiratory depression of overdosage with sodium pentothal, but does not raise the fatal dose or shorten the duration of sleep (R. W. Whitehead *et al.*, 1946).

The *picrotoxin* should be injected intravenously at the rate of 3 mg. in 1 cc. of saline per minute, until the corneal reflexes reappear and the patient can be roused by pain stimuli; then sufficient to keep the patient somewhat restless, about 3 to 6 mg. per hour. Severe cases require 100 to 150 mg., mostly during the first day (J. P. Anderson, 1941), but sometimes as high as 1820 mg.

The proof of the effectiveness of convulsants against barbiturates is based on *animal experiments.* It is difficult to demonstrate by direct evidence that picrotoxin has saved human lives, because the fatality of untreated cases varies widely and overlaps that of treated cases. Maloney, 1933, showed that optimal dosage of picrotoxin (3 mg. per Kg., intravenously for rabbits) is more effective against barbiturates than optimal doses of strychnine (1 mg. per Kg., vein), or cocaine (20 mg. per Kg., hypodermically). Barlow, 1935, found that picrotoxin (usually in 5 or 6 doses) saved 60 per cent of the rabbits poisoned with two and a half times the normally fatal intravenous dose of pentobarbital and 30 per cent with three and a half fatal doses. In those that died, the time to death was lengthened to four or five times the untreated. All analeptic agents caused symptomatic improvement of pentobarbital, chloral and avertin narcosis. The superiority of picrotoxin over the other analeptics is probably due to its more prolonged stimulation of the respiration, lasting for one-half to three hours with picrotoxin, one-quarter to three-quarter hour with metrazol (Barlow, 1938).

Intracisternal injection of picrotoxin (0.023 to 1.2 mg. per Kg.), in dogs, was reported by Rice and Isenberger, 1936 and 1937, more effective than intravenous injection against the narcosis and respiratory paralysis produced by intracisternal injection of sodium amytal (2.6 to 7.8 mg. per Kg.); ephedrine sulfate, 1.3 to 2.9 mg. per Kg., was also much more effective cisternally than by vein; but coramine and metrazol were not effective antagonists by this route.

Succinate of sodium has been reported an effective antidote to barbiturate narcosis (Soskin and Taubenhaus, 1943; Pinschmidt *et al.*, 1945). Others report discordant results. K. H. Beyer and Latven, 1944, found little effect. It has no effect on dogs; in cats it apparently rather increases the toxicity and narcosis (S. Krop, 1946). It does not antagonize chronic phenobarbital intoxication (P. J. Hanzlik, 1945). *Clinically,* it is reported to produce dramatic awakening from deep pentothal anesthesia. Intravenous injection of 2 to 200 cc. of 30 per cent solution of disodium succinate hexahydrate causes the patients to cough within fifteen to thirty seconds; the skin flushes deeply in thirty to 120 seconds; the respiration is temporarily increased; the patient is awake and oriented in ten to fifteen minutes if the dosage was adequate. There were no untoward symptoms. Succinate has also proved effective in attempted suicide by other barbiturates and by morphine. Intravenous injection of 5 cc. of 10 per cent succinate solution into normal subjects causes flushing, sometimes succeeded by pallor; and a feeling of suffocation twenty to thirty seconds after the injection (C. J. Campbell *et al.*, 1946). The trial of succinate was based on the observation of Quastel and Wheatley that the oxidation of succinate by brain mash is not depressed by barbital, as is that of dextrose, lactate and pyruvate.

Data on rabbits indicate an inverse relation of the *pyruvate level* of the blood and barbiturate depression. The antagonism appears to be functional, as the rate of destruction is not decreased (B. A. Westfall, 1946).

Diuretic Treatment.—The slow and prolonged excretion of barbital prompted the trial of sodium chloride and glucose diuresis, but they proved ineffective intravenously (Gower and Tatum, 1929), and only slightly more effective by mouth (Gower and Van de Erve, 1933). Intravenous ammonium chloride greatly accelerates the elimination of barbiturate, but it has little effect on the narcosis (Koppanyi and Murphy, 1934).

Habitual Use of Barbiturates.—The use of somnifacient, sedative or excitant drugs may become habitual with persons of a certain neurotic disposition, and this bent may take the direction of morphine, alcohol, chloral or barbiturates or all of these, according to circumstances. Chronic insomnia is the most common occasion for starting the use of barbiturates; a considerable number employ them for tranquilization or euphoria; a few for "sprees." A certain amount of psychical adaptation is readily acquired, as with alcohol; but there is little real tolerance for large doses; nor are they liable to the severe withdrawal reactions characteristic of morphine, although about a third of the subjects develop craving if the drug is withheld (Hambourger, 1940). The dependence is psychic, not physical (Tatum, 1939). Prolonged use may develop psychical degeneration and mania, as with alcohol, but these are often absent after long-continued daily administration. The minor grades of mental aberration seriously increase industrial hazards (Drysdale, 1939). Somewhat over half of the states have enacted laws regulating the sale of barbiturates, and these generally include chloral, sulfonal and their derivatives.

The prevalence of barbiturate addiction is difficult to judge, except by its widespread consumption, but a large part of this is used occasionally rather than habitually. However, a single druggist sentenced in New York had sold 50,000 tablets in three years as intoxicant "goof pills" (Federation Bulletin, 1944, *30*:212). The survey by Hambourger, 1940, indicates that barbiturates constituted 10 per cent of all addiction cases, exclusive of alcohol, admitted to the selected group of larger general hospitals; but pronounced addiction is still a curiosity. Acute poisoning by overdosage, generally suicidal, is fairly frequent among the addicted (Taddei, 1913).

Tolerance by Habituation.—Considerable adaptation to the narcotic effects develops rather rapidly, in man and in animals, the sleep being shortened by a third to a half, and the subsequent hebetude is much lighter. The lethal dose, however, is not altered materially (C. M. Gruber and Freedman, 1945; Ettinger, 1938; Stanton, 1936). Sleep-tolerance induced by one barbiturate generally extends to the others. It is rapidly lost on discontinuing the administration (C. M. Gruber and Keyser, 1946).

Withdrawal Symptoms.—After administering barbiturates to rats daily for seven weeks, Stanton, 1936, found no increase of restlessness in withdrawal, in contrast to morphine; indeed, the animals accustomed to barbiturates were less resentful to tying. Seconal and amytal were similarly negative (Phatak and Hill, 1941). A few patients, especially those with marked addiction, have one to three *convulsive seizures* after sudden or gradual withdrawal, but without permanent ill effects (C. W. Osgood, 1947).

Chronic barbiturate poisoning may produce nervous abnormalities: vertigo, ataxia, nystagmus, mild dementia, visual hallucinations, motor paralyses, tremor; and gastro-intestinal irritation, anemia and tremor, hematoporphyrinuria (Krep, 1905; A. Lambert, 1915). It may also reveal partly controlled mental aberrations and thus simulate encephalitis, acute psychic depression or delirium tremens. The mental symptoms improve on withdrawal, but ten weeks may be required to clear them completely (S. Weiss, 1936; Seevers and Tatum). Prolonged administration of large doses of phenobarbital to rats has no measurable effect on maze learning and retention (M. R. Jones and Jones, 1942), unless the effects approach the fatal (G. W. Williams and O'Brien, 1937). Depressant doses, however, stunt the growth more than does diphenylhydantoin (Hanzlik, 1945).

PREPARATIONS.—The barbiturates occur as white crystalline powders of somewhat bitter taste. The free acids are but slightly soluble in cold water, fairly soluble in hot water, and soluble in alcohol. They may be taken by mouth, in capsules, tablets, or dissolved in hot liquids. The sodium salts are freely soluble in water, but the solutions decompose on standing.

The following lists the more common barbiturates in alphabetic order:

Alurate, allylisopropyl barbituric acid. Dose, 65 to 130 mg.; *Tablets*, 65 mg. *Alurate sodium tablets*, for preanesthetic, equivalent to 0.2 Gm.

Amytal, isoamylethyl barbituric acid; tablets of 8, 16, 50 and 100 mg. Dose, as sedative, 20 to 40 mg. two or three times daily; as hypnotic, 0.1 to 0.3 Gm.; preanesthetic, 0.2 to 0.6 Gm.; tetanus, 0.4 to 0.8 Gm. *Sodium Amytal*, also suitable for intravenous injection; *ampuls* of 0.065, 0.125, 0.25, 0.5 and 1 Gm.; "*pulvules*" of 0.06 and 0.2 Gm.; *suppositories* of 0.2 Gm.

Barbital, U.S.P., diethylbarbituric acid (*veronal*, *barbitone*). Dose, as hypnotic, 0.3 Gm. *Barbital Tablets*, U.S.P.; usually 0.3 Gm. *Barbital Sodium*, U.S.P. (*medinal*); *Tablets*, U.S.P.; usually 0.3 Gm.

Dial, diallylbarbituric acid. Dose, as sedative, 30 mg.; as hypnotic, 0.1 to 0.3 Gm.; *Tablets*, 30 and 100 mg.

Hexobarbital Soluble, *Evipal Sodium*, evipan, cyclural, endodorm; N-methylcyclohexenyl methyl barbiturate. Dose: see under intravenous anesthesia. *Ampuls* contain 0.5 or 1 Gm. as powder.

Ipral Calcium, ethylisopropyl barbiturate. Dose, 0.12 and 0.25 Gm. *Tablets* of 50 and 120 mg. *Ipral Sodium Tablets* of 0.25 Gm.

Neonal, n-butylethyl barbituric acid. Dose, 0.05 to 0.4 Gm. *Tablets* of 0.1 Gm.

Nostal, isopropyl bromallyl barbituric acid. Dose, as sedative, 50 to 100 mg.; as hypnotic, 0.1 to 0.3 Gm. *Tablets* of 0.1 Gm.

Ortal Sodium, n-hexylethyl barbiturate. Dose, 0.2 to 0.4 Gm. *Capsules* of 0.05, 0.2 and 0.3 Gm.

***Pentobarbital Sodium**, U.S.P., ethyl (1-methyl-butyl) barbiturate (*nembutal*). Dose, as hypnotic, 0.1 Gm.; preanesthetic, 0.2 Gm. *Capsules*, U.S.P.; usually 30 and 100 mg.

***Pentothal Sodium** (See Thiopental Sodium, U.S.P.)

Pernoston, butyl-B-bromallyl barbituric acid. Dose, as hypnotic, 0.2 Gm. *Tablets* of 0.2 Gm. *Pernoston Sodium.* Dose; see under intravenous anesthesia. *Ampuls* of 2 cc. of 10 per cent.

Phanodorn, cyclohexenyl ethyl barbituric acid (cyclobarbital). Dose, as hypnotic, 0.1 to 0.4 Gm. *Tablets* of 0.2 Gm.

***Phenobarbital**, U.S.P., phenyl ethyl barbituric acid (*luminal*). Dose, 0.015 to 0.2 Gm. *Tablets*, U.S.P.; usually 15, 30 and 100 mg. *Elixir*, U.S.P., with 17.5 per cent of alcohol. Dose, 4 cc., contains 16 mg. of phenobarbital. *Phenobarbital Sodium*, U.S.P.; *Tablets*, U.S.P., usually 30 and 100 mg.

Sandoptal, isobutyl allyl barbituric acid. Dose, as hypnotic, 0.2 to 0.8 Gm. *Tablets* of 0.2 Gm.

***Seconal Sodium**, allyl (methyl propyl carbonyl) barbiturate. Dose, as hypnotic, 0.1 to 0.2 Gm.; preanesthetic, 0.2 to 0.3 Gm. "*Pulvules*" of 0.05 and 1 Gm.; *suppositories* of 0.13 Gm.

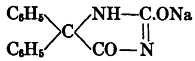
***Thiopental Sodium**, U.S.P. (**Pentothal Sodium**, Thiopentanone), ethyl (1-methylbutyl) thiobarbiturate; soluble in water, but the solution decomposes on standing. Dose; see under intravenous anesthesia. *Sterile Thiopental Sodium*, U.S.P., a mixture of thiopental sodium and anhydrous sodium carbonate as buffer, containing at least 91.7 per cent of thiopental sodium. Usually available in ampuls of 0.5, 1.0 and 5 Gm.

Navigan is a sedative pyridine derivative, with actions similar to the barbiturates (Krautwald *et al.*, 1939).

HYDANTOINS

These differ from the barbiturates in having an acetic instead of a malonic acid residue. The only two of importance at present are phenylethyl hydantoin (nirvanol), which has been used in chorea; and diphenylhydantoin (phenytoin, N. N. R., dilantin), which is used against epileptic convulsions. Both may produce marked side actions, apparently with capillary injury, which restricts their application.

Phenytoin Sodium (*diphenylhydantoinate, dilantin, epanutin*)



is an effective anticonvulsant with relatively weak somnifacient action. It was introduced by Merritt and Putnam, 1938, for the treatment of epilepsy, originally on the basis of its anticonvulsant action in animals. Clinically, it controls grand mal, including the jacksonian, more effectively than petit mal, preventing the convulsive seizures or decreasing their number and severity, without causing hebetude or lethargy, differing in this respect from barbiturates or bromide. It is therefore less disturbing, and it succeeds in many cases where these sedatives and ketogenic diet have failed; but it does not effect a cure. The effects disappear within two days after its administration is stopped. It must be continued indefinitely, and this is often difficult because of its side actions. It should be used only under close medical supervision after milder measures have failed. It is more effective if it is given along with phenobarbital. It has no effect on chorea (O. P. Kimball, 1939). Schizophrenia and nonepileptic psychoses may be improved by diminished excitement and irritability, but only during the administration (Kalinowsky and Putnam, 1943).

The *anticonvulsant actions of sedatives* were compared by Merritt and Putnam, 1938, on cats convulsed by an interrupted electric current passing from the mouth to the occiput. These convulsions closely resemble those of grand mal, and remain constant from day to day, in untreated animals. Phenobarbital proved effective, but more favorable ratios of anticonvulsant:soporific effect were found with several newer drugs, especially diphenylhydantoin, acetophenone, acetophenoneoxime, benzophenone and propiophenone. A series of nonhypnotic sulfoxides and sulfones was found effective against electric convulsions in cats, but appeared without material advantage over diphenylhydantoin (Merritt, Putnam and Bywater, 1945). Barbiturates other than phenobarbital were but little effective, as was also bromide in doses which proved fatal on continued administration (Merritt, Putnam and Schwab, 1938). Morphine and acetylsalicylic acid do not change the threshold in rabbits (Tainter *et al.*, 1943). With this technic, Knoefel, 1940, found the threshold for convulsions raised 50 per cent by phenyl-hydantoin in $\frac{1}{10}$ of the fatal dose. Other studies of anticonvulsant series are reported by Knoefel and Lehman, 1942; Kozelka *et al.*, 1942; L. Goodman and Toman, 1945.

Phenytoin materially raises the threshold for convulsions that follow reduction of high barometric pressure (E. C. Hoff and Yahn, 1944). It has little if any effect on petit mal seizures in patients, and does not raise the threshold to metrazol seizures, nor does it prevent electroencephalographic dysrhythmia of subconvulsive metrazol doses or electric shock (Goodman, Swinyard and Toman, 1946). Its action appears to be cortical, for it does not raise the threshold for electric convulsions in decerebrate cats (Knoefel and Lehman, 1942). The spinal reflexes are augmented. Cocaine and strychnine convulsions are not antagonized. Large doses may cause convulsions followed by prolonged extensor rigidity (Knoefel, 1940).

The abolition of the tonic phase of the major seizures of electroshock is a better criterion of clinical antiepileptic efficiency than is the raising of the convulsive threshold (J. E. P. Toman *et al.*, 1946).

Isopropyl alcohol increases the effectiveness of diphenylhydantoin against electroconvulsions (R. L. Driver, 1947). Among a considerable series of derivatives, the *diisobutyl-hydantoin* approached the diphenyl in potency (W. C. Chu and Driver, 1947). Methyl phenylethyl hydantoin, "mesantoin," is clinically equivalent to diphenylhydantoin against grand mal, without producing muscular incoordination or gingival hypertrophy; but many patients develop a generalized rash and somnolence (W. G. Lennox, 1946).

Administration in Epilepsy.—Phenytoin sodium has a bitter taste. It is administered in capsules with a glass of water after meals. The dosage should be the smallest that prevents the seizures, as determined by individual trial, beginning with 0.1 Gm. three times daily and increasing gradually, if necessary, to double this dosage (W. G. Lennox, 1942).

Minor side actions occur in almost all patients, generally between the third and tenth day of treatment. They are chiefly nervous, such as ataxia, vertigo, blurred vision, nystagmus, tremors, dysphagia, insomnia or somnolence, irritable temper, sometimes mental confusion and hallucinations. Electrocardiogram changes also appear in the majority, but disappear on discontinuing. The strongly alkaline reaction of the drug may produce gastric irritation (Finkelman and Arieff, 1943). These symptoms call for temporary reduction of dosage; some patients must be kept below 0.4 Gm. daily.

Hyperplastic gingivitis (first reported by O. P. Kimball, 1939) develops in about half the patients under long-continued phenytoin treatment. It is a low grade inflammation, beginning with warty rippling of the gingivamucosal surface, and progressing to a firm, painless hyperplasia, with proliferation of the capillaries and connective tissue and round cell infiltration. It is a progressive complication, which returns but slowly to normal. It is rarely sufficient, however, to necessitate discontinuance of the drug. It may be treated by excision. Dental care helps, but does not prevent (L. Stern *et al.*, 1943). It differs from the gingivitis of scurvy, which is not hyperplastic (Ziskin *et al.*, 1941), and it is not due to deficiency of *ascorbic acid* (Merritt and Foster, 1940), nor has it any significant effect on the utilization of ascorbic acid (Emmett *et al.*, 1943).

More serious toxic reactions consist chiefly in dermatitis, dry skin, itching, rash and purpura. Morbilliform or scarlatinous dermatitis occurs in 5 to 15 per cent of the patients after nine to fourteen days of administration. It calls for temporary withdrawal, but generally no harm results if the drug is continued. Serious exfoliative dermatitis has occurred after forty days, but is rare. Purpura has been observed in a patient after two months of treatment. No changes of liver or kidney functions or blood cell count have been found, but caution is advised in its use in cardiorenal and debilitated patients (Merritt and Putnam, 1938; Kimball, 1938).

Other Effects of Phenyl-hydantoin on Animals.—The toxicity is much greater by vein than by mouth. Intravenous injection of 25 mg. per Kg. for rabbits produces marked fall of blood pressure (also in spinal dogs), depression of the vagus nerve and respiration, and death by respiratory paralysis. Uterine movements are inhibited; excised uterus of nonpregnant rabbits is relaxed by 1:150,000. Parenteral injection of excessive doses into mice, rats, rabbits and dogs causes erethismus, spastic gait, exophthalmos, accelerated respiration and convulsions (M. E. Drake *et al.*, 1939; Haury and Drake, 1940; C. M. Gruber *et al.*, 1940). *Continued feeding* to rats is less injurious than is phenobarbital (Hanzlik, 1945).

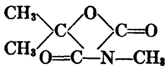
The *concentration of phenytoin in the blood* of patients receiving 300 mg. daily amounts to 3 to 6 mg. per 100 cc. The concentration *in the tissues* of rabbits injected intravenously with 50 mg. per Kg. is highest in the liver, decreasing in the sequence of brain, kidney, blood and muscle (Kozelka and Hine, 1938). In man and dog, about two-thirds of the administered quantity is completely destroyed; only 1 to 4 per cent is excreted unchanged in the urine; small quantities are metabolized to the corresponding hydantoic and amino acid (Kozelka and Hine, 1943; Knoefel and Lehman, 1942).

PREPARATIONS—**Diphenylhydantoin Sodium,** U.S.P., **phenytoin,** N.N.R.; epanutin, B.P.; *dilantin.* White odorless powder, freely soluble in water, giving a somewhat turbid alkaline solution. *Average dose,* 0.1 Gm. *Capsules,* U.S.P., of 30 and 100 mg.

Phenylethyl-hydantoin (*Nirvanol*), $C_6H_5.C_2H_5.C-(CONH)_2$, was originally introduced as a somnifacient sedative, and was found to produce marked improvement in some cases of chorea, but proved dangerous because it often causes febrile and exanthematous reactions, and lymphocytosis and eosinophilia, which set in when the administration has been continued for a week or two. Metabolic changes occur even in the absence of pyrexia, with temporary retention, first of water, then of Na and Cl, finally of K (Rockwell, 1935). The skin reactions are often excessive, beginning with cyanotic swelling of the face, high fever (above 40°C.), excessive macular and papular exanthemata, swelling of the eyelids, suppurative conjunctivitis and stomatitis (review, Pilcher and Gerstenberger, 1930). Its use is therefore not generally advisable. The levorotatory form is more potent than the dextro to produce nirvanol sickness (B. Schick, Sobotka and Peck, 1933).

"TRIDIONE" (TRIMETHADIONE)

This substance is 3,5,5,-trimethyl oxazolidine-2,4-dione:



It is analgetic, mildly sedative, and selectively anticonvulsant; generally controlling the petit mal, myoclonic and akinetic seizures characterized by "spike and wave" electroencephalograms. It improves 83 per cent of the patients, and suppresses the seizures in 31 per cent. It terminates status epilepticus, but is ineffective against grand mal convulsions, though it sometimes reinforces diphenylhydantoin (Lennox, 1947). Its mode of action is not known. The improvement sometimes persists after stopping the medication (W. G. Lennox, 1945; De Jong, 1946). It is not soporific, and the petit mal triad against which it is effective also responds to caffeine and amphetamine, which are not otherwise sedative.

Tridione was synthesized by M. A. Spielman, 1944. Its analgetic and anticonvulsive actions were first reported by Everett and Richard, 1944.

In animals, nondepressant doses of tridione raise the threshold of metrazol seizures more than barbiturates. It is more potent than phenytoin against electroshock convulsions. Residual effects of single doses persist for two days (L. S. Goodman, Swinyard and Toman, 1946). Intravenous injection relaxes tetanus (R. K. Richards, 1947). It is the most potent analgetic of the oxazolidine-2, 4-dione series (Everett and Richards, 1944).

Side effects are chiefly a functional mistiness of vision on going into a bright light. This occurs in nearly a third of the patients, in a few days to ten days of administration. It generally disappears a week or ten days after discontinuing. Sometimes the eyeball is painful. There are no anatomic changes, and the action is not explained. It is less frequent in children (Lennox, 1947).

Skin rashes are also fairly frequent, gastric irritation less so.

The most serious, but fortunately infrequent, side actions are *aplastic anemia* and fatal granulocytopenia. The drug should therefore be carefully supervised. It should not be used if there is a history of blood dyscrasias (R. P. Mackay and Gottstein, 1946; F. F. Harrison *et al.*, 1946).

Administration.—The usual dosage in pyknoepilepsies is 1 to 2 Gm. per day in divided doses, as 0.3 Gm. capsules. It may be advisable to decrease the amount if the photophobia is annoying. If grand mal is also present, phenytoin, phenobarbital or bromide may be added.

PREPARATIONS—**Trimethadione, Tridione,** N.N.R., is a white crystalline solid of a slight camphoraceous odor; slightly soluble in water, readily in alcohol. Evaporates rather readily. Marketed as *Tridione Capsules,* 0.3 Gm.

Benzimidazole, investigated by L. Goodman *et al.*, 1943, has a selective depressive effect on the tonus of skeletal muscle, on postural reflexes and on voluntary motion. The action is central, and mutually antagonistic with metrazol.

SYSTEMIC ACTION OF GASES

Gas may act (1) mechanically, by excluding oxygen from the lungs; this is the case with the "indifferent gases," such as nitrogen, hydrogen and methane; (2) as local irritants, as do halogens (bromine, chlorine), gaseous acids (sulfurous, nitrous) or alkalis (ammonia); (3) systemically after absorption, as do other dissolved substances, by their specific actions. The irritant and anesthetic gases are considered under these headings (see Index).

Humphry Davy was one of the first to make extensive trials of gases with the object of developing therapeutic applications. He experimented on himself with N, H, N_2O, and CO (as water gas) and nitric oxide, with more enthusiasm than discretion, and had some narrow escapes (F. C. Bing, 1933).

The systemic effects of gases depend quantitatively on their concentration in the blood; this, when equilibrium has been reached, is the simple product of the partial pressure in the alveolar air and the solubility coefficient for blood plasma. The *rate of absorption* of a given gas is directly proportional to its concentration in the air breathed, the rate of the pulmonary ventilation, and the rate of the pulmonary circulation. The last two factors are more important for the easily soluble gases. The absorption rate decreases in a logarithmic curve as the concentration in the blood approaches equilibrium. The attainment of equilibrium between alveolar air, blood and tissues depends on the duration of the inhalation, as well as on the partial pressure and the *solubility*. With low concentrations equilibrium is attained so slowly that the duration of the inhalation becomes a major factor in the blood concentration.

The partial pressure of a gas at normal barometric pressure is equal to the volume-percentage of the gas. The effect of the normal percentage of oxygen at half an atmosphere is the same as that of half the percentage at ordinary pressure; conversely, 1 per cent of a gas at 3 atmospheres produces the same effect as 3 per cent at 1 atmosphere.

The *concentration of gases in air may be expressed* either as parts by volume (per cent, per thousand, or per million, "ppm"), or as weight per volume (mg. per liter), or as partial pressure (per cent volume × 7.6 mm. Hg). "Ppm" may be transposed to "mg. per liter" by multiplying by the molecular weight × 0.0000409 (based on 22.4 liters as the volume of one gram-molecule of gases at 0° C., 760 mm.). The *solubility coefficient* is the amount of gas in solution needed to balance a given partial pressure of the gas. It varies with the nature of the fluid, decreases with rise of temperature, and is independent of the pressure of other gases. It is expressed as the amount of gas (calculated as cubic centimeters at 0° C., 760 mm.) in a liter of the solution. Gas solubility in blood plasma is slightly lower than in water (about 10 per cent), approximately by the amount of solid substances. This holds also for lipo-soluble gases. The solubility of a gas may be expressed as the *coefficient of distribution*, the relative weight of gas in equal volumes of fluid and of the gas mixture to which this is exposed (for instance, concentration in fluid = 12 mg. per liter; in air = 3 mg. per liter; distribution coefficient = 12:3 = 4).

Rapidity of Action.—The effects of gases appear promptly after beginning the inhalation, and disappear as rapidly when the animal is made to respire pure air. This is due to the large surface and large alveolar surface of the lungs, and the large quantity of blood that circulates through the alveolar capillaries; for the whole blood passes through the lungs every thirty seconds. As these factors are relatively greater in small mammals, these succumb and recover much more rapidly than man, and may indeed be used as a test of the safety of suspected air. While the recovery from the direct effects of gases is rapid, indirect after-effects may be persistent.

Equilibrium of Blood and Tissues.—The gases pass from the blood into the tissues, and in the reverse direction, according to the relative concentration and solubility coefficient, speeded or restrained by the rate of blood flow and restricted to some extent by the difficult permeability of the cell surface (particularly in adipose tissue). The *average solubility of most gases in most tissues* is about proportional to their water content, and therefore slightly lower than in the blood plasma; but the concentration at equilibrium approaches fairly closely to the product of the concentration of the gas in the air × its solubility coefficient at body temperature.

When the tissues are taking up gas from the blood, the concentration in the arterial blood is higher than in the venous. The difference decreases as equilibrium is approached. When the inhalation has been stopped, the gradient of gas concentration is reversed, so that it passes from the tissues to the venous blood, to be excreted into the alveolar air, and the concentration in the arterial blood is lower than that of the venous. In either case, the concentration of the venous blood approaches most closely that in the tissues. The increase and decrease in the tissues follow exponential curves. The half-saturation time is a convenient criterion for comparisons of the speed of absorption and elimination, as it is independent of the concentration of the gas. This time increases with the solubility of the gas. With a man at rest, it requires about two and one-half hours for ether, and only seven minutes for nitrogen. Tissues with rapid circulation (the brain, viscera and glands) reach equilibrium much sooner than those of slower circulation (the muscles, bone and fat). The spleen is also slow, as it is largely outside the active circulation (Henderson and Haggard, "Noxious Gases").

Absorption of gases from the intestines is active. When 60 cc. of various gases were injected into a ligated 25 cm. loop of small intestines of anesthetized cats, the absorption rate per hour averaged: CO_2, 160 cc.; H_2S, 69 cc.; O_2, 14 cc.; H_2, 7.5 cc.; CH_4, 4.3 cc.; N_2, 1 cc. Similar results were obtained from the colon. The low absorption of nitrogen is due partly to its slight solubility, partly to the fact that the blood and tissues are already four-fifths saturated with nitrogen. If atmospheric air is injected into the intestines, the volume diminishes rapidly until the oxygen has been absorbed, then slowly. Parallel with the absorption of the injected gases, there is also *diffusion of other gases into the lumen;* for instance, after intestinal injection of 100 per cent oxygen, the gas remaining after an hour contained 73.5 per cent of O_2, 5 per cent of CO_2 and 21.5 per cent of N_2. In two hours, the percentage of nitrogen had risen to 33 per cent. Two hours after an injection of hydrogen, the gas contained 45 per cent of H_2, 10 per cent of O_2, 5 per cent of CO_2 and 40 per cent of N_2 (McIver, Redfield and Benedict, 1926). *Postoperative gas distention is* due largely to the faulty propulsion of swallowed air. McIver, Benedict and Cline, 1926, found the percentile composition of the rectal gases similar in postoperative surgical distention and in medical cases, as follows: nitrogen, 49 to 92, indicating the important share of swallowed air; hydrogen, 0 to 34 (median about 3); carbon dioxide, 3.8 to 14 (about as in venous blood); methane, 0 to 19 (median about 3); oxygen, 0 to 9.4 (median about 1.5); hydrogen sulfide, present in only one patient of the thirteen.

CARBON DIOXIDE (CARBONIC ACID)

This acts as a weak acid, producing locally rather mild irritation; and after absorption, strong medullary stimulation; in higher concentrations, narcosis. These actions play the principal role in ordinary asphyxia. Deficiency of CO_2 (acapnia) leads to corresponding depressant phenomena. The carbonic acid therefore acts as a hormone (Bayliss and Starling, 1906) which regulates the activities of various functions, especially of the respiration. In this way the CO_2 tension of the blood and tissues is normally kept automatically at a practically constant level.

Its function in neutrality regulation will be considered under that heading (see Index).

Local Actions.—CO_2 as gas or solution produces a prickling sensation and reddening of the skin and mucous membrane, followed by numbness and local anesthesia. The sensory irritation leads to reflex stimulations (Quincke, 1877). The cutaneous stimulation is utilized in the form of carbonated baths (Nauheim baths), especially in cardiac diseases. Frozen CO_2 (carbon dioxide snow) is employed as a superficial cauterizant. In the stomach, carbonated water ("soda water") hastens absorption, increases the secretion of acid gastric juice (Chiari, 1915), and acts as a carminative. It is useful against nausea, and valuable for disguising the taste of medicines. Experimentally, it produces marked augmentation of the gastric contractions and of the pyloric discharge. This is apparently due to parasympathetic stimulation, for it can be prevented by atropine (Carnot and Koskowski, 1922).

Normal CO_2 Exchange.—Inspired air contains normally physiologically insignificant amounts of CO_2 (0.04 vol. per cent). In the alveoli it enters into equilibrium with the gases of the blood (by purely physical diffusion, *not* by active secretion), losing part of its oxygen and gaining carbon dioxide, which is constantly formed by the combustion of the body. The concentration of CO_2 in the expired air is about two-thirds that of the alveolar air, as about one-third of the tidal air does not reach the alveoli because of the "dead space."

Normal CO_2 percentages and tensions are approximately as follows, per cent as volume, tension as mm. Hg: expired air, 4 per cent, 30 mm.; alveolar air, 4.6 to 6.2, average 5.5 per cent, 42 mm.; arterial blood, 36 to 40 per cent, 30 to 42 mm.; venous blood, 45 to 50 per cent, 30 to 50 mm.; tissue, 51 to 58 per cent, 40 to 70 mm.

Condition of the CO_2 in the Blood.—Blood contains 3 to 4 volumes per cent of CO_2 in physical solution; the remainder, yielding about 50 volumes per cent, ocurs in the plasma and corpuscles in combination. In the plasma it exists as bicarbonates, chiefly as $NaHCO_3$, partly as protein bicarbonate, and H_2CO_3. The greater part is in the red blood corpuscles as $KHCO_3$ and chiefly as hemoglobin bicarbonate or carbamate (Roughton, 1935, review), chloride diffusing out into the plasma in exchange (Van Slyke, Wu and McLean, 1923), so that considerable CO_2 may be added to the blood with little change in the *p*H of the plasma (L. J. Henderson, 1920). The corpuscles contain a catalase, *carbonic anhydrase,* which accelerates the reaction between CO_2 and water in both directions ($CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H.HCO_3$) (Meldrum and Roughton, 1933). It contains about ⅓ per cent of zinc as an essential constituent (Keilin and Mann, 1940). The epithelium of the parietal cells of the *gastric mucosa* is especially rich in carbonic anhydrase, which is probably instrumental in the secretion of hydrochloric acid (H. W. Davenport and Fisher, 1940; W. Ashby, 1944).

Carbonic anhydrase also plays an essential role in the urinary tubules, and in the shell-forming organ of birds (H. W. Davenport, 1946, review).

Oxygen on CO_2 of Blood.—Oxygen (and carbon monoxide) tends to expel CO_2 from the blood; for when exposed to a given CO_2 tension, blood that has been deprived of oxygen takes up considerably more CO_2 than oxygenated blood (Christiansen *et al.*, 1913). CO_2 or lowering of *p*H decreases the oxygen-binding power of hemoglobin. It is disputed whether CO_2 combines with hemoglobin like oxygen.

Carbon dioxide *diffuses rapidly into cells* from alkaline solutions, and turns their reaction toward acid (Jacobs).

Diffusion Through Skin.—The uptake and output of CO_2 into the water of baths follows the gas diffusion laws. Hyperemia increases the exchange by 4 or 5 times (Kramer and Sarre, 1936). The ratio of diffusion $CO_2:O_2$ through *various animal membranes* differs widely: At 100 mm. Hg pressure difference it averages 8.2 for eggshell membrane, 25 for frog lung, 35 for rabbit peritoneum (Lin and Tsai, 1939).

Effects of CO_2 Inhalation in Man.—If oxygen deficiency is excluded by inhaling gas mixtures containing 20 per cent of oxygen, no effects occur until the concentration approaches 2 per cent of CO_2 by volume, when the breathing becomes deeper, and the tidal volume is increased 30 per cent, the minute volume 5 per cent (Haldane and Priestley 1905). With 4 per cent of CO_2, the depth of the respiration is greatly increased and the rate slightly quickened, with considerable discomfort. With 4.5 to 5 per cent the breathing becomes extremely labored, almost unbearable for many individuals. The tidal air rises to about 10 liters per minute, with 2 mm. rise of the alveolar and arterial CO_2 tension (Douglas and Havard). Nausea may occur. With 8½ per cent of CO_2 there is distinct dyspnea, rise of blood pressure and congestion, which become insupportable in fifteen or twenty minutes, but disappear promptly in fresh air. The limit of tolerance is 7 to 9 per cent. The respiratory stimulation culminates about 10.4 per cent (E. W. Brown, 1930); about 15 per cent in animals (Zuntz, 1897). Above 10 to 11 per cent, ataxia develops, followed by unconsciousness, in about ten minutes. The symptoms increase to 15 per cent; but even 20 per cent is not dangerous in an hour to animals, and probably not to man; but depressed patients may be much more easily injured. With 25 to 30 per cent, the stimulant phenomena pass into depression, with diminished respiration, fall of blood pressure, coma (generally without convulsions), loss of reflexes, anesthesia, and gradual death after some hours by pulmonary edema and hemorrhage. The heart outlasts the respiration. With higher concentrations, the stimulation is still briefer. With pure CO_2, death may occur in a few minutes as a mixed effect of carbon dioxide and anoxemia. *Daily exposure* of an hour to 8 per cent CO_2 did not have marked deleterious effects (Tomaszewski *et al.*, 1937).

Rats always survive abrupt exposure to 10 per cent; a few die at 15 per cent; few survive 20 per cent; at 25 per cent half die within six hours, none survive thirty-six hours (M. H. Seevers, 1944). Much higher concentrations are tolerated if the concentration is gradually increased than with sudden exposure; the acclimatization is attributed to diminished oxygen consumption. If the external temperature is low, 5 per cent of CO_2 produces reversible narcosis (J. H. Barbour and Seevers, 1943).

Share of CO_2 in Ordinary Asphyxia.—When asphyxia occurs by respiratory obstruction or by breathing in a confined space, the accumulation of carbon dioxide is solely responsible for the early symptoms, the dyspnea and distress; the fatality is due solely to the oxygen deprivation.

Respiration.—The CO_2 content of the blood is the chief regulating factor in ordinary respiration (Zuntz, 1897; Douglas and Havard), the respiratory center being stimulated (mainly the rate) even by very slight increase of the CO_2 tension. A rise of 0.2 per cent of CO_2 (1.6 mm.) above the normal percentage of the alveolar air (5.6 per cent) doubles the respiration, and a slight reduction (0.2 per cent) of the CO_2 produces apnea. The sensitiveness to oxygen is much less, the respiration being unaffected by variations of the oxygen in the air between 13 and 100 per cent (Haldane and Priestley, 1905; Fitzgerald and Haldane, 1905). The effective increase of CO_2 also produces a slight but measurable change in the hydrogen ion concentration of the blood (Campbell and co-workers, 1913). Other acids are similarly stimulant (Winterstein, 1911; Laqueur and Verzár, 1911), although not quite so much (Hooker *et al.*, 1917), because they penetrate cells less readily (Douglas and Havard). The hyperpnea of muscular exercise is due to CO_2 rather than *p*H changes (review, J. H. Comroe, 1944). Loevenhart, 1913, referred the effects ultimately to interference with oxygenation. The response to CO_2 is used experimentally as a test of the excitability of the respiratory center (A. Loewy, 1890). Concentrations above 15 per cent depress the respiration (Lowry and Zuntz, 1897). *Bronchial muscle* (*excised*) is constricted by moderate, relaxed by high, concentrations (Trendelenburg, 1912).

Medullary Centers in Asphyxia.—The effects are alike whether they result from CO_2, acidosis or oxygen deprivation. The stimulation occurs in the order of respiratory, then vasomotor and then vagus centers. It is followed by depression of these centers. The relative preponderance of stimulation and depression depend on the degree and suddenness of the asphyxia, and on the prevailing condition of the centers (Loevenhart, 1915). The stimulating effects are due largely to reflexes from the carotid body, but the medullary depression is direct.

Asphyxial Reflexes from the Carotid Sinus and Cardiac-Aortic Regions.—Increase of CO_2 or increased hydrogen ion concentration of the blood and decreased oxygen concentration stimulate the respiration and vasomotor center through these reflexes. Heymans *et al.* report that these are sensitive to smaller changes than are required for direct stimulation of the centers. The opposite changes in the concentration produce the opposite reflexes. Comroe and Schmidt, 1937, concluded that the hyperpneic response to CO_2 and acid is much more central than reflex, but that oxygen deficiency acts mainly or entirely by reflex.

The respiratory ventilation of insects is materially increased by 15 per cent of CO_2.

CO_2 on Circulation.—Increase of carbon dioxide from 3 to 25 volumes per cent in the inspired air causes a marked rise of blood pressure, mainly by stimulation of the vasomotor center. Moderate increase of CO_2 tension perhaps also increases the output of the heart. The central constrictor stimulation is exerted chiefly on the splanchnic vessels. The vessels of the skin are passively dilated. The peripheral action on blood vessels results in their dilatation. Concentrations above 25 per cent lower the blood pressure by depression and finally paralysis of the vasomotor center and heart (Hill and Flack, 1908; van Esveld, 1930).

Vasomotor Center.—Violent stimulation was proved by Sollmann and Pilcher, 1911, and by Mathison, 1911. The latter demonstrated that identical effects are produced by other acids and by lack of oxygen, and that all these act probably by increasing the hydrogen-ion concentration of the blood. The spinal vasomotor centers are much less sensitive than the medullary (Mathison, 1910). The stimulation of the vasomotor center by increase of carbon dioxide or acidity or by deficiency of oxygen is chiefly reflex from the carotid sinus (C. Heymans, Bouckaert *et al.*, 1932). The vasoconstriction involves mainly the splanchnic vessels.

Direct Action on Vessels.—Perfused or excised vessels are dilated by physiologic concentrations of CO_2, such as stimulate the respiratory center (Bayliss, 1901; Hooker, 1912). Very high concentrations may constrict (Fleisch *et al.*, 1932). A similar dilatation is produced by other weak acids (Schwarz and Lemberger, 1911). Barcroft, 1914, considered this an important factor for the increase of local circulation in active organs, especially with the rise in blood pressure resulting from the sinus reflex. Bernthal and Shoemaker, 1937, however, claimed that CO_2 is purely constricting to blood-perfused dog legs, and that decrease below the normal CO_2 level (43 mm.) causes dilatation.

Pulmonary Circulation.—The pressure in the pulmonary arteries rises in asphyxia, even if the rise of the systemic blood pressure is prevented by destroying the medulla (Wood, Jr., 1911). The pulmonary circulation time is slowed (Langlois and Desbouis, 1912), indicating pulmonary vasoconstriction.

Venous Pressure.—Increase of carbon dioxide causes a large rise of venous pressure, even when the arterial pressure is but little affected. Henderson and Harvey, 1918, interpreted this as due to direct dilatation of the capillaries and venules.

Efficiency of the Heart.—In intact animals, the cardiac effects are complicated by the other actions. In dogs whose heart rate, venous return and arterial tension were kept constant, Wiggers, 1929, found that changes of alveolar CO_2 between 15 and 60 mm. had no effect on the ventricular contractions, so that the changes ordinarily observed would be indirect. The *heart rate* is ordinarily slowed by stimulation of the vagus center; but if the vagi are divided, it is quickened by stimulation of the accelerator center (Dastre and Morat, 1885). Ketcham, King and Hooker, 1912, found that the *isolated heart* is depressed by all concentrations. Jerusalem and Starling, 1910, claimed that increase of CO_2 in the coronary blood lessens the tonus both in systole and diastole. The coronary vessels are also dilated (Markwalder and Starling, 1913). With higher concentrations, the systolic tonus is lowered more, so that the excursions are diminished; with moderate concentrations, the diastolic tone is more relaxed and the output increased. A certain concentration would therefore be necessary for the optimum efficiency of the heart; this is insufficient in acapnia. Perfusion of the coronary vessels of a mammalian heart with CO_2 gas causes prompt fibrillation and arrest, whereas the heart continues to beat for a considerable time if the perfusion is made with oxygen, or even hydrogen (Magnus, 1902).

The *blood viscosity* is somewhat increased by CO_2, but not to an important degree (Burton-Opitz, 1911). The *erythrocyte volume* is increased by CO_2 in passing from the arteries to the veins, and decreased when CO_2 is lost in the lungs. Under the influence of CO_2 the *erythrocytes* take up chloride from the serum, and increase its alkalinity. Similar changes occur in hemolysis (Rohonyi and Lorant, 1916). Increased acidity diminishes the *affinity of hemoglobin* for oxygen (or carbon monoxide); with a carbon dioxide tension of 40 mm., the oxygen percentage must be doubled to secure the same degree of saturation (Barcroft, 1914).

Protoplasm Consistency.—The fluidity is first increased by CO_2, then decreased. Accordingly, the protrusion of *pseudopodia* is first favored, then arrested (M. H. Jacobs, 1922).

Peristalsis.—In intact animals this is stimulated by asphyxia. Excised intestine is started to rhythmic contraction if it was quiescent; but is relaxed if it was already rhythmically active (Hooker, 1912). Inhalation of 50 per cent carbon dioxide inhibits cecal peristalsis induced in rabbits by physostigmine or pilocarpine (J. Auer and Krueger, 1942).

Oculomotor Center.—The pupils are ordinarily widely dilated by asphyxia, after primary constriction (Guthrie and Ryan, 1910). The mydriasis occurs after division of the cervical sympathetic (Braunstein, 1894). It must therefore be ascribed to inhibition of the oculomotor center. Peripherally, CO_2 constricts frogs' pupils (Auer, 1909).

Convulsants.—Strychnine convulsions may be suppressed by CO_2 inhalation (Ryan and Guthrie, 1908). On the other hand moderate asphyxia increases the convulsant effect (Pilcher). Concentrations above 20 per cent also heighten the susceptibility to acid fuchsin convulsions (Joseph, 1915). Conversely, picrotoxin, lobeline and camphor appear to make animals more subject to CO_2 convulsions (Wieland and Mayer, 1922).

Temperature.—CO_2 dyspnea lowers the temperature in health, and especially in fever. It also reduces metabolism (v. Magyary-Kossa, 1910).

Hyperglycemia.—Inhalation of carbon dioxide increases the blood sugar, even when given with oxygen. The effect may be partly directly on the splanchnic innervation of the liver, partly indirectly through augmented epinephrine output, and probably also directly on the liver cells (Cordier, 1934).

Deficiency of CO_2 (Acapnia).—The carbon dioxide tension regulates the heart rate, vascular tone, peristalsis, mental condition and a number of other functions. A decrease of this tension in the blood and tissues causes depressant effects.

The *phenomena of acapnia* were emphasized especially by Y. Henderson, 1908 to 1910. Even a slight reduction of the CO_2 causes marked increase of the heart rate and slowing of respiration. Further reduction produces tachycardia, venous stasis, arrest of peristalsis, failure of many reflexes, coma and stoppage of respiration. Extreme reduction causes an almost tetanic condition of the heart, abolishing its output, lowering blood pressure and resulting in death. In the lighter grades, recovery occurs promptly if the CO_2 tension is increased, as by breathing through a long tube.

Acapnia resulting from *pulmonary hyperventilation* promptly produces dizziness, blurred vision, numbness of the extremities. If long continued, it causes muscular spasms of the face, hands and feet, sometimes opisthotonos, generalized convulsions and unconsciousness. Physical and nervous fatigue may persist for some days (E. C. Schneider, 1930; R. Harwood, 1938).

Acapnia and Respiration.—The respiratory center is readily depressed by deficiency of CO_2 in the blood. This is the main factor in the apnea following hyperpnea, and one factor in Cheyne-Stokes respiration (Haldane, 1905, 1909). The increased oxygen content, to which it was formerly attributed, seems to be unessential, although excessive oxygen concentration is also depressant (Loevenhart, 1913). The direct depressant effect of CO_2 deficiency on the respiratory center was demonstrated by Winterstein's (1911) *perfusion experiments.* The respiration was not restored by oxygen, but by carbonic or other acids, and is therefore a hydrogen ion effect. In intact animals a persistently low oxygen tension leads to the accumulation of lactic and other acids, and hence to stimulation of the respiration.

Apnea.—Suspension of the respiratory movements is usually due to depression of the respiratory center by excessively low CO_2 content of the blood (acapnia); for instance, as a consequence of hyperpnea. Fredericq showed that apnea can be produced by the transfusion of the blood of an apneic animal. Acapnia is not essential, however, for excessive distention of the lungs may produce apnea even when the air contains 5 per cent of CO_2. This phenomenon does not occur if the vagi were divided (Githens and Meltzer, 1914). In fowls, CO_2 deficiency also stops the respiratory movements, but the effect consists in tonic spasm of the respiratory muscles, and not in heightened threshold. The function of CO_2 would therefore consist in the maintenance of the respiratory rhythm (Meyer and Meltzer, 1915).

Therapeutic Use of Carbon Dioxide and Oxygen Inhalation.—The stimulant actions of carbon dioxide on respiration and on the vasomotor centers may be utilized in acute respiratory depression by the inhalation of oxygen containing 5 per cent of CO_2. Stronger concentrations, 7 to 10 per cent, become detrimental if inhaled longer than a few minutes. A well fitting mask with appropriate valves is indispensable. This has been used especially in the treatment of *carbon monoxide poisoning.* The deeper and more rapid respiration raises the percentage of oxygen in the alveolar air, so that it may displace the CO more promptly, which is also fanned out of the lung more effectively. Brief inhalation may be useful to ventilate excess of *volatile anesthetics* from the lung (Henderson, 1924; Waters, 1933), but continued administration, as by rebreathing, tends to postanesthetic pneumonia (Waters, 1938). It improves respiration in *poisoning by alcohol, methyl alcohol or morphine* (Henderson, 1924), but it cannot be continued sufficiently to be of much benefit. It is undesirable in pneumonia and *pulmonary and cardiac disease,* because of the discomfort and exertion (Boothby, 1932; D. J. Cohn *et al.*, 1939).

Inhalation of 10 per cent CO_2 with 90 per cent oxygen may be used to dislodge adherent bronchial mucus (A. L. Benyai and Cadden, 1943). Y. Henderson, 1932, advocated inhalation for carbon dioxide in the paroxysmal stage of *pertussis,* 6 or 7 per cent in air or oxygen, for ten or fifteen minutes once or twice daily for eight days, to cause deep breathing, distend the lungs and clear the air passage, thus diminishing the incidence of pneumonia.

Psychiatric Conditions.—Very short inhalation of 30 per cent carbon dioxide in oxygen, resulting in anesthesia, may produce a remarkable, but only temporary, clearing of the psyche in paralytic *dementia* (Loevenhart). Similar temporary improvement is obtained in schizophrenia. Inhalation of 5 per cent carbon dioxide has been tried against *catatonia,* but without success (de Jong, 1934).

PREPARATION—***Carbon Dioxide,** **U.S.P.** (*Carbonei Dioxidum*), is 99 per cent by vol. of CO_2. Usually supplied in metallic cylinders.

OXYGEN

The oxygen inhaled as air replaces that which is used up in the combustion of the tissues. It is carried by the hemoglobin, and restores venous to arterial blood. It constitutes about one-fifth (20.94 per cent), by volume, of ordinary air. An increase of this proportion, and even the inhalation of undiluted oxygen, produces no noticeable effect under ordinary conditions. The rate of *oxidation* or the consumption of oxygen is not increased (Pflueger); indeed, the output of CO_2 is rather lessened. Evidently the proportion of oxygen in air suffices for all ordinary needs (or, rather, it is greater than necessary); additional oxygen acts as an indifferent gas. In other conditions, however, namely, when the supply of oxygen is deficient from any cause, its inhalation removes the asphyxial symptoms with striking promptness and efficiency.

Historical.—Oxygen was discovered by Priestley in 1744. Its function in respiration was shown by Lavoisier in 1777. The history of its first therapeutic use, also that of nitrous oxide, by Beddoes, 1798, is reviewed by A. H. Miller, 1931.

Condition of the Oxygen in the Blood.—The effects of most gases are directly proportional to their partial pressure in the respired air. Oxygen departs from this rule, for there are practically no further effects when its percentage is raised above 10 per cent. This is explained by the fact that only a small part of the oxygen is carried in physical solution in the blood plasma. By far the greater part is in loose chemic combinations with hemoglobin, 1 molecule of hemoglobin combining with 1 molecule of O_2 (Butterfield, 1913). When respiring ordinary air without obstruction, the hemoglobin of the arterial blood is already over nine-tenths saturated with oxygen, and the amount taken up can be but little increased by raising the oxygen tension (Buckmaster and Gardner, 1913). The oxygen of the plasma increases directly with the oxygen percentage of the alveolar air, but the amount thus carried is small, 0.6 per cent (Haldane, 1917).

The *dissociation curve of oxyhemoglobin* follows the law of mass action, showing that the reaction is chemic, and not adsorptive. The curve is identical for pure solutions of hemoglobin, whatever their origin, but it is affected by electrolytes, and therefore differs in the blood of different animals or even individuals. Increased acidity diminishes the affinity, and therefore the effective concentration of oxygen. The same holds for CO-hemoglobin (Barcroft, 1914). Hemoglobin dissolved in plasma combines with oxygen ten times faster than when it is enclosed in the corpuscles (Jacobs), but it is less effective as an oxygen carrier.

Oxygen Concentrations of Air and Blood.—The following represent the usual values:

	Volume of O_2 Per 100 Cc.	Pressure of O_2, mm. Hg	Per cent Saturation of Hemoglobin
Inspired air.......	20.9	158	
Alveolar air.......	14.5	110	
Expired air.......	16.4	125	
Arterial blood.....	19.5–20.6	100–105	92–98
Venous blood (right heart)....	14	35–40	64–81
Tissues (approximate)...	....	20–40	

The *absorption of oxygen in the lungs* is simply physical under ordinary conditions; but if so much CO is inhaled that the supply of oxygen to the tissues becomes inadequate, there is an active (secretory) absorption, so that the partial pressure of oxygen in the arterial blood becomes higher than in the alveolar air. This occurs also when the demand for oxygen is increased by muscular work. It is not known how this correlation is brought about (Douglas and Haldane, 1910).

Excessive Oxygen Concentrations.—The inhalation of pure oxygen produces no immediate effects, even with pressure of 4 atmospheres; but injuries develop gradually and progressively if the partial pressure exceeds 60 per cent of an atmosphere; the speed and severity depend on the concentration of the oxygen, and on the age of the individual, young subjects being less susceptible. It is inadvisable to inhale undiluted oxygen for more than a few hours at a time, or to use concentrations higher than 65 per cent if the administration is to be prolonged indefinitely. Continuous sojourn in 80 to 100 per cent oxygen is innocuous for twenty-four to forty-eight hours, but longer exposure may result in pulmonary irritation, edema and pneumonia (J. Lorrain Smith, 1899). Higher pressures, 3 or 4 atmospheres, may be tolerated for a time, but after about three hours serious symptoms appear, including peripheral vasoconstriction, visual changes, rise of blood pressure, convulsive seizures terminating in death by paralysis of the respiratory and cardiovascular centers. If the subject is restored to ordinary air before death, recovery occurs immediately or within an hour.

Minor Effects of Oxygen Inhalation.—Cl. Bernard claimed that birds placed in pure oxygen are greatly excited, and that the urine of rabbits becomes acid.The *efficiency* of athletes is increased, and forced respiration can be maintained longer (Hill and Flack, 1909, 1910). Christiansen and co-workers, 1913, attributed this to the smaller solvent power of blood for CO_2 in the presence of excess of oxygen. Lavoisier and Seguin, 1789, reported that pure oxygen has no effect on *metabolism.* This has been confirmed by modern investigators.

Toxic Effects of 67 to 100 Per Cent of Oxygen.—Results differ somewhat quantitatively with animal species, age and other conditions, even when complicating impurities are excluded. Partial pressures *below 60 per cent* appear to be tolerated indefinitely (53 per cent for three and a half days; Karsner and Ash, 1917). Normal men show no symptoms when exposed to 50 per cent for twenty-four hours (J. R. Comroe *et al.*, 1945). Most animals are not affected by 60 per cent, but some developed severe pulmonary injury, although they did not die in a week of exposure (J. A. Campbell, 1927). Rabbits remained well for three months, except for a decrease of about 15 per cent in hemoglobin and in red cell count (Barach, 1926). Between *67 to 80 per cent* most animals develop pulmonary congestion and inflammatory changes, usually not fatal. Rabbits exposed to 67 per cent for eleven days showed slight pulmonary irritation; 80 per cent usually produced no change in twenty-four hours, but definite damage in forty-eight hours (Karsner, 1915), and pulmonary edema in two or three weeks (Barach, 1926). About half of normal men inhaling 75 per cent oxygen for twenty-four hours show some symptoms (J. R. Comroe *et al.*, 1945). Dogs exposed to 80 per cent for a week became ill, but not fatally. Exposure to 90 per cent killed by pulmonary edema within five days (J. R. Paine *et al.*, 1941).

Undiluted (100 per cent) oxygen is probably safe for all patients for brief administration, but not beyond twelve hours. Inhalation for twenty-four hours by a large number of normal men produced substernal distress, significant decrease of vital capacity, often with nose and throat irritation. Intermitting the administration for fifteen minutes every three hours did not diminish these effects (J. R. Comroe *et al.*, 1945). Dogs exposed to 100 per cent oxygen developed respiratory distress within forty-eight hours and died in about sixty hours, the lungs showing extreme congestion, interstitial edema and polymorphonuclear infiltration (J. R. Paine, 1941). *Guinea pigs* in 80 to 100 per cent oxygen develop marked dyspnea and die with gasping respiration. Their bronchioles to and excluding the alveoli show tumefaction and necrosis, resembling phosgene poisoning (J. Pichotka, 1941). *Humidity and heat* both increase the toxicity of oxygen (H. R. Hulpieu and Cole, 1944). Considerable resistance to oxygen intoxication may be induced by *habituation*, either by gradual increase from 60 to 100 per cent, or by intermittent exposure to 100 per cent for fifteen minutes four times daily (A. L. Barach *et al.*, 1944). *Differences in the threshold of injury concentration* are due at least partly to the much greater resistance of *young individuals* (Smith, Thompson and Drinker, 1932). This applies also to *compressed air.* Young rats tolerated indefinitely sojourn in air at 4 atmospheres (equivalent to 86 per cent of oxygen at ordinary pressure). In older rats, symptoms of acute pulmonary hyperemia began on the fourth day. A few died, generally in about a week, at most in two weeks. If this period is survived, adaptation occurs and the animals recover, although remaining in the compressed air, and tolerate further exposure indefinitely (two hundred and seventy-two days). If rested and again exposed, there is no recurrence of the acute symptoms. The difference in age susceptibility is connected with age differences in the structure of the normal lung (Smith, Thompson and Granville).

Compressed air injury, more properly decompression injury (*caisson disease*), is due to the mechanical injury of the central nervous system by the liberation of nitrogen bubbles during rapid decompression. The damage is especially marked in nervous structures because fats and lipoids dissolve more nitrogen than does water.

Compressed Oxygen.—Paul Bert found 3 to 4 atmospheres very toxic to animals. The symptoms resemble those of asphyxia (review, J. W. Bean *et al.*, 1945). *Healthy men* can breathe *oxygen at 3 atmospheres* for three hours without distress. During the fourth hour visual symptoms appear, progressive contraction of the visual field, mydriasis and some impairment of central vision. These are associated with signs of peripheral vasoconstriction, culminating in the fourth hour in abrupt rise of systolic and diastolic pressure, increase of the pulse rate, extreme pallor of the face, dizziness, sensation of impending collapse, and partial stupor. Prompt and complete recovery occurs on restoration to normal air (Behnke, Forbes and Motley, 1936). *Anesthetized dogs exposed to oxygen at 4 atmospheres* for three hours show blood pressure changes, convulsive seizures of the head and neck, death by paralysis of the respiration, with depression of the cardiovascular centers. *Increase of CO_2* accentuates and hastens oxygen poisoning, even with CO_2 concentrations innocuous at atmospheric pressure (Shaw, Behnke and Messer, 1934). *Rats* exposed to 5 or 6 atmospheres of oxygen for fifteen to twenty minutes may have convulsive seizures, followed by spastic paralysis which is sometimes permanent. Repeated exposures spaced to permit symptomatic recovery produce additive effects, increased acute central nervous response and persistent motor dysfunction, attributed to tissue damage (J. W. Bean and Siegfried, 1945). Anesthetized rats die by apnea in a little over an hour when exposed to 6 atmospheres of oxygen; somewhat later if hyperventilated (J. W. Bean, 1945). These effects are not due to pressure as such, for they are not produced by compressed air until the partial pressure of oxygen reaches these figures. The high pressure of oxygen interferes with the reduction of blood hemoglobin by the tissues, entailing inadequate liberation of base to carry away carbon dioxide, and so resulting in acidosis (J. W. Bean, 1931). It also poisons the respiratory enzymes of the cells directly (J. W. Bean and Bohr, 1938). Paul Bert, 1878, also showed that oxygen above 3 or 4 atmospheres pressure is fatal to *tissues.* It is toxic to *unicellular organisms,* beginning at about 1½ atmospheres, probably by interfering with respiratory enzyme processes (J. W. Bean, 1941). Excised *frog heart* responds to 5 or 6 atmospheres of oxygen by initial increase in the force of ventricular contractions, followed in a few hours by slight weakening and slowing, then cessation of automatic contractions. It remains excitable to electric stimulation much longer (Bohr and Bean, 1939). *Carbon dioxide production by skeletal muscle* is first increased, then decreased, and is reversible by decompression; the effects are not produced if the pressure is increased by addition of nitrogen (R. E. Cass, 1945). *Excised intestine* of rabbits is also depressed and paralyzed, reversibly, by oxygen at 5 atmospheres, apparently by direct action on the muscle (Bean and Bohr, 1940).

OXYGEN DEFICIENCY

The most important phenomena connected with oxygen arise from its deficiency, *anoxia*, through inadequate access to the lungs (asphyxia), unsaturation of the hemoglobin (anoxemia), deficiency of the hemoglobin (anemia), inadequate circulation (ischemia), or incapacity of the tissue cells to utilize oxygen (histologic anoxia, as in cyanide poisoning).

Etiology.—Asphyxia by obstruction of the air passages or by breathing in a confined space involves hypercapnia as well as anoxia. Pure anoxia without carbon dioxide accumulation results from breathing rarefied air or air diluted with indifferent gases, nitrogen, hydrogen, methane, and so forth; by carbon monoxide, which displaces oxygen from hemoglobin; or by agents that convert hemoglobin into methemoglobin. Anoxemia without carbon dioxide accumulation may also exist in pneumonia and cardiac decompensation when obstruction of a part of the lungs is compensated by overventilation of other parts; this washes out the excessive carbon dioxide, but does not materially increase the oxygen saturation of the mixed blood (R. G. Pearce, 1917).

The symptoms of anoxia develop so insidiously that the subject may be unaware of them. They arise chiefly from stimulation and depression of the central nervous system, since this is most susceptible to oxygen deficiency. The course depends upon the duration as well as the degree of the deficiency. Ordinary air may be diluted until it contains about 15 per cent of oxygen (or may be rarefied to the same degree), without producing any immediate effect (Bernstein, 1882). A candle is extinguished when the oxygen has fallen to about 17.5 per cent, and is therefore a test for the safety of the air, as far as oxygen is concerned. At about 10 per cent slight symptoms are noticeable, especially on exertion, but they are not alarming—dizziness, shortness of breath, deeper and more frequent respiration, quickened pulse, slight cyanosis. With 7 per cent, these symptoms become serious, and stupor sets in. With a slightly lesser percentage, unconsciousness occurs; 5 per cent is the minimal concentration compatible with life. With 2 to 3 per cent death occurs within forty-five seconds. Different persons vary in sensitiveness to oxygen deficiency or to mountain sickness (N. E. Baxter *et al.*, 1944). Patients with cardiac and pulmonary disease are more susceptible because their compensation is impaired; thyrotoxic patients develop anoxia more easily because of their greater oxygen consumption. Conversely, hypothyroid subjects are more tolerant. This has been confirmed experimentally on animals (Asher and Durand; Asher and Streuli).

Minor grades of oxygen deficiency have been studied by the Air Service Medical Research Board, because of their importance in aviation. It was found that even slight lowering of the oxygen tension produces reactions to compensate for the diminished oxygen supply of the tissues (Y. Henderson and Seibert, 1918). The chief reactions are increased ventilation of the lungs and more rapid blood flow. In a few men there is also concentration of the blood. The *differences in tolerance* depend upon the completeness of these reactions. Some tolerate 6 per cent of oxygen for brief periods; others are incapacitated by much smaller changes. The degree of tolerance and the reactions is an objective test of general "fitness," and is diminished by any indisposition, colds, worry, and so on (Schneider, 1918). The relation of *age and sex* was investigated by R. F. Kline and Britton, 1945, on various mammals. Fetal and newborn animals are very resistant to reduction of barometric pressure. Adult females resist a fourth to a half longer than males, especially in the cold. *Estrous* conditions and *castration* do not appear related to the difference. Petit mal loss of consciousness occurs in epileptic patients when the inspired air contains 8 to 12 per cent of oxygen; high oxygen pressures induce convulsions (W. G. Lennox and Behnke, 1936). Full narcotic doses of *alcohol* reduce the lethal effects of acute anoxia in mice; amytal and pentobarbital do not produce much effect. Some *cholinergic* and *sympathicolytic agents* have a limited prophylactic value. Adrenergic and para-sympathicolytic agents tend to increase the fatality rate (G. A. Emerson and Van Liere, 1943; standardized technic for testing). Polycythemia produced by *transfusion* does not increase resistance to reduced barometric pressure (P. Wetzig and D'Amour, 1943).

Henderson and Haggard group the phenomena of anoxia into *four stages*, best marked when they develop slowly. The *first stage* starts when the oxygen of the inspired air is reduced to 16–12 per cent. It begins with increased volume of respiration, which lowers the CO_2 concentration of the blood. The pulse quickens. Attention and clear thinking require more effort. Muscular coordination for skilled movements is somewhat diminished. The *second stage*, with oxygen reduced to 14–9 per cent affects the higher brain centers, resembling alcoholic inebriation. Some subjects become exhilarated, talkative or quarrelsome; with emotional outbursts or fixed ideas. Some complain of headache or numbness. Voluntary coordination and attention are impaired, but perception, memory and discriminative judgment may remain good. Burns and bruises are not noticed. Muscular efforts fatigue readily, the subject may faint. The respiration is often of Cheyne-Stokes type (which always denotes anoxemia; Douglas and Haldane). The *third stage*, with oxygen range of 10 to 6 per cent, exaggerates the earlier symptoms. Nausea and vomiting may set in. Vigorous movements become impossible. There is ascending paralysis of motion, then of sensation. The patient is bewildered and does not realize that anything is seriously wrong until his "legs give way" and it is too late to escape. He may then realize that he is dying, but is indifferent. Consciousness is lost, with amnesia on revival. In the *fourth stage*, with oxygen below 6 per cent, the respiration stops, convulsive movements occur and the heart is arrested six to eight minutes after the respiration.

Abrupt anoxia results in immediate loss of consciousness. The symptoms are seen clinically *when nitrogen is administered* for three or four minutes in *treating schizophrenia* where the arterial oxygen is reduced to about 2 per cent (volume). They begin with progressive stimulation of the respiration; then progressive tachycardia, to about 160 per minute, with various types of arrhythmia. The systolic blood pressure rises progressively. Muscular twitching starts about the face, followed by generalized clonic contractions, tetanic opisthotonos, or extensor torsion. Consciousness is lost about the time when the twitching appears. Urinary incontinence is exceptional. Cyanosis is relatively late and never intense. One or two inflations with oxygen produce prompt and complete recovery from this acute anoxia (F. A. D. Alexander and Himwitch, 1939). *With somewhat slower anoxia*, the recovery is also slower, and is likely to leave sequels, hallucinations, excitement, headache, often with nausea, depression and apathy, which may increase for several hours and last till next day. These phenomena are attributed to pressure from cerebral edema. They may be temporarily relieved by intravenous injection of hypertonic sugar or salt solution. If the anoxia is more severe or prolonged, *organic degenerative changes* occur in the nervous system, especially in the cerebral cortex and basal ganglia (Steegmann, 1939). These result in persistent paralyses, amnesia, and so forth. These are especially common after carbon monoxide poisoning, since its anoxia is more persistent. Pulmonary congestion is frequent, probably owing to circulatory changes. Pneumonia is also a frequent and indirect sequel. Degenerative lesions may be produced in the myocardium, aorta, testes and bone marrow. Anoxic changes occur also under various conditions which interfere with the oxygen supply to the tissues; in shock of all varieties, and in poisoning by carbon monoxide or dioxide, convulsants, digitalis, epinephrine, histamine, nitrites. *Mountain sickness* corresponds to the second and third stages of anoxia as described above. *Airplane nausea* is also partly anoxic, and patients with cardiac or pulmonary disease or thyrotoxicosis should be cautioned against high flying.

Injury to the nervous centers by anoxia has been studied in dogs and cats by occlusion of the cephalic circulation. Consciousness, corneal reflex and respiration are arrested within forty seconds; in six to eight seconds if the oxygen supply of the brain is suddenly reduced, so that the oxygen saturation of the blood of the internal jugular vein, which is normally 60 per cent, falls to 24 per cent (Lennox, Gibbs and Gibbs, 1933). If the occlusion lasts not longer than two minutes, recovery is complete within a few hours, without histologic changes. If it lasts ten minutes or longer, the animal does not come out of coma; if the anoxia lasts eight minutes or less, consciousness returns within forty-eight hours; but permanent sequels follow if the anoxia lasts three and one-quarter to five minutes. They are due to degenerations of the nervous structures, necrosis and softening of the cortex, especially of the motor and visual areas. Laminae 3 and 4 are the most vulnerable. Purkinje cells of the cerebellum rank next to the cortex. The geniculate are the most vulnerable of the basal ganglia. The brain stem and spinal cord are not injured (L. M. Weinberger *et al.*, 1940; C. Dennis and Kabat, 1939).

C. Heymans and Bouckaert, 1938, report that the respiratory, vagus and vasomotor centers of the dog can be revived after thirty minutes of total suspension of their circulation. The pupillary and corneal reflex centers are revivable after ten to fifteen minutes; some other centers only to five minutes, with later death following muscular rigidity, coma and hyperthermia.

The *vulnerability of the nervous centers* may be explained by the *high oxygen consumption* of the brain, amounting to about 13 cc. of oxygen per 100 Gm. of wet brain weight per minute (Himwich and Nahum, 1932), or about 8 per cent of the total oxygen consumption of the body (C. A. Handly *et al.*, 1943). The oxygen consumption of brain tissue suspensions is not affected by reducing the oxygen tension to 4 mm. Hg (K. A. C. Elliott and Henry, 1946). *Monoiodoacetate* inhibits the oxidation of glucose by the brain *in vitro*, but has little effect on the oxidation of lactate, pyruvate, glutamate or succinate (Quastel and Wheatly, 1934).

Medullary Centers in Anoxia.—These are stimulated by moderate deficiency of oxygen, and paralyzed by extreme oxygen deficiency. The respiratory center is the most sensitive, then the vasomotor, and least the vagus center. The stimulation is partly direct, but chiefly reflex from the carotid sinus (Heymans *et al.*, entirely so, A. G. H. Bjurstedt, 1946; the depression is direct. The intensity of the reaction is determined by the rapidity and degree of the change and by the state of the centers. Excessive oxygen is depressant.

The *resiratory response* generally starts at about 16 to 14 per cent of oxygen and becomes marked with 12.5 to 9 per cent. It usually affects the depth more than the rate; indeed, the rate may stay unchanged, especially if the reaction is good (Schneider, 1918). It begins with hyperpnea, followed by decreased amplitude when the overventilation has lowered the CO_2 tension. The decrease of CO_2 may be useful, as it increases the oxygen capacity of hemoglobin.

Haldane, 1919, stated that the first response of anoxemia is *periodicity of the respiration*. With further reduction, the type becomes rapid and shallow. Patients with "irritable heart" are especially likely to react in this way to exertion. Oxygen inhalation gives relief. *Cheyne-Stokes respiration* is also referable to oxygen deficiency (Douglas and Haldane, 1909); the apnea lowers the oxygen and leads to accumulation of lactic acid. This increases the excitability of the respiratory center, so that a low CO_2 tension suffices to produce hyperpnea. This lowers the CO_2 and increases the oxygen, so that the lactic acid is oxidized, apnea reappears and the whole process is repeated.

The *blood pressure* shows several types of response. *If the reaction is good,* it may be unchanged; if the heart quickens, the systolic pressure may rise and the diastolic fall gradually. *If the reaction is poor,* the systolic pressure falls suddenly, soon followed by fall of diastolic pressure and then slowing of the heart. These phenomena are often accompanied by fainting (Schneider, 1918).

Heart.—Reduction of the partial pressure of oxygen to 14 per cent increases the rate and diastolic volume of the heart, with increased minute output. These effects increase to 11.5 per cent of oxygen, and the rate increases further to 7 per cent oxygen (Hilton and Eichholtz, 1925). The *coronary vessels* are markedly dilated in asphyxia, anoxia and myocardial anemia, increasing the diastolic and especially the systolic coronary flow (H. D. Green and Wégria, 1942). The response to electric stimulation of the peripheral stump of the divided vagus is increased (Danilewsky and Wyalkowa, 1931). *When the capacity of response is exceeded,* the heart may either slow or quicken by 50 to 90 beats (Schneider, 1918). *Temporary heart failure* is not uncommon. It is shown by dilatation, also followed by collapse and fainting, unless the oxygen is increased (Whitney, 1918). The *terminal cardiorespiratory crisis* starts with great vagal slowing, preventable by atropine. This is followed by irregularities due to functional changes in the conducting system. Cardiac decompensation then causes abrupt fall of the arterial and rise of the venous pressure, accompanied by severe depression and final arrest of the respiration.

The blood vessels (including the coronaries) are dilated by anoxemia, on direct perfusion (Richards, 1914). Oxygen deficiency also lowers the tone of excised arteries (Roncato and Oselladore, 1923). *Capillaries* likewise are dilated by deficiency, and constricted by excess tension of oxygen (Krogh). Carbon dioxide dilates the capillaries and arteries, but low concentrations of CO_2 may be somewhat stimulant (Roncato and Oselladore).

Digestive Tract.—Reduction of partial oxygen pressure to 43 mm. depresses the hunger contractions and the digestive peristalsis of the stomach. It has no effect on the motility of the small intestines; the colon is somewhat more sensitive. There is little effect on gastric or intestinal secretion, or on intestinal absorption (E. J. Van Liere *et .,al* 1944).

The *oxygen consumption of smooth muscle* is rather slow. It is increased by rhythmic contractions, and by temperature rise within physiological limits. It is not increased, but rather is diminished when the tonus is raised by drugs. It is depressed but not abolished by cyanide (C. L. Evans, 1923). *Excised smooth muscle organs* suspended in Locke's solution require continuous aeration in order to function. The stirring of the solution by the air bubbles helps to remove carbon dioxide and to bring oxygen to the surface of the tissue, so that even nitrogen or hydrogen is effective for a time (Evans and Underhill, 1923; Simonart, 1926), but they soon become harmful (Gross and Clark, 1923).

The pupillary dilatation in anoxia is due chiefly to diminished tonus of the oculomotor centers. Epinephrine and sympathetic stimulation play no part (Gellhorn and Levin, 1945).

Disturbances of Vision.—These are among the minor manifestations of oxygen deficiency (Wilmer and Berens, 1918) and are probably due to the disturbed circulation. Rats exposed to severe anoxia develop lens opacities (J. G. Bellows and Nelson, 1943).

Cyanosis.—The reduced hemoglobin of oxygen deficiency gives a cyanotic tint to the skin and mucous membranes. (A similar but more intense blue is conferred by methemoglobin and sulfhemoglobin.) The unsaturation may occur through incomplete aeration in the lungs, through slowed peripheral circulation, or through excessive oxygen consumption in the tissues. In ordinary asphyxia involving increase of carbon dioxide, superficial vessels are dilated, giving a *blue cyanosis;* an ashen-gray cyanosis is characteristic of anoxemia without hypercapnia, as in mountain sickness, shallow breathing, acute pulmonary edema of "gassing" and pneumonia (Haldane, Meakins and Priestley, 1918). Ischemia, as in surgical shock and in anemia, gives a pallid blue tint.

Ordinarily, cyanosis is just detectable in the finger nails and lips when 10 per cent of the hemoglobin of the arterial blood (or 30 per cent capillary blood) is unsaturated; it is definite with 15 per cent, and marked with 20 per cent of unsaturation (Stadie). The intensity and depth are also materially influenced by the amount of blood in the capillaries and veins of the area (Lundsgaard, 1918, 1919).

The cyanosis of reduced hemoglobin is distinguished from that of methemoglobin in that it may be caused to disappear by increasing the local blood flow, as by placing an arm in a bath at 45° C. (Meakins and Davies, 1920). The color of the venous blood coming from an organ depends upon the flow. That from the submaxillary gland is black when the gland is resting, red when it is functioning. The blood of the renal vein is normally always red (Cl. Bernard).

Asphyxial Glycosuria.—All forms of asphyxia, whether from CO_2 or deficiency of oxygen, lead to hyperglycemia and glycosuria. This does not occur if the liver is excluded, or in poorly nourished animals (W. Auel, 1914). It requires the cooperation of the adrenals, for it does not occur if these have been excised (Macleod, 1913). *Basal metabolism* is first increased by the greater respiratory exercise of oxygen deficiency. It decreases with the depression.

Oxygen Deprivation in Treatment of Schizophrenia.—The measures used therapeutically to impress schizophrenic patients involve decrease of cerebral oxidation: insulin by diminishing the fuel dextrose; metrazol and other convulsants by producing anoxemia; cyanide (Loevenhart) by poisoning the oxidative function of the cells. This does not appear to be the chief mechanism, however. Himwich *et al.*, 1939, reported encouraging results by pure anoxia produced by inhaling nitrogen; but others have failed to obtain a therapeutic response (L. R. Sillman and Terrence, 1943).

Accommodation to Acute Oxygen Deficiency.—Brouardel claimed that an animal asphyxiated slowly revives much more readily than one asphyxiated abruptly. Similar observations have been made clinically. *Newborn infants* and animals also resist asphyxia (by drowning or strychnine) much longer than adults. Newborn babies have been revived after ten to fifteen minutes of immersion ("Les Asphyxies," p. 13).

Chronic oxygen deficiency, as seen in anemias, and the like, causes increased tissue destruction, fatty degeneration, acidosis and general paralysis of all organ functions. Exposure to slightly rarefied air, as on mountains, causes "*mountain sickness*"—nausea, headache, insomnia, and so forth. This generally disappears after a few days. Henderson and Haggard attribute these symptoms to hyperventilation, resulting in alkalosis. A curious phenomenon is a prompt and persistent increase in the corpuscles and hemoglobin content of the blood (by 25 to 40 per cent). This is at first due to diminution of the plasma, the total quantity of hemoglobin being unaltered. After a time the absolute hemoglobin is also increased by stimulation of the formation of corpuscles by the bone marrow (G. H. Martin *et al.*, 1916). The respiratory metabolism is increased. These effects are attributed to oxygen deficiency (Douglas; Haldane, Henderson and Schneider, 1913). *The accommodation is limited:* Mice and rabbits, which are highly resistant to oxgyen deficiency, remain healthy indefinitely and continue to grow normally in 12 per cent oxygen; but in 10 per cent oxygen (equivalent to 20,000 feet altitude) growth ceases promptly, the weight decreases, the animals are sickly, and many die in four or five weeks, with chronic cardiac hypertrophy. Some show tetany, with normal or high serum calcium (J. A. Campbell, 1935). In rabbits, exposure to this altitude for sixteen hours daily, for five days a week, promptly induces polycythemia (J. Goodman, 1947).

Acute clinical asphyxia, such as is produced by obstruction, by breathing in a confined space, or by arrest of the heart, involves both accumulation of carbon dioxide and deficiency of oxygen; the hypercapnia is responsible for the air hunger and other early symptoms, and the anoxia for the final fatality. *When asphyxia occurs rapidly,* three typical stages may be distinguished: During the *first stage,* the respirations (particularly the inspirations) are increased. In the *second stage,* the respirations are irregular and convulsive, the inspirations shallow and weak, the expirations powerful and prolonged. Consciousness is lost. The skin, especially the face, becomes cyanotic. The *third stage* is characterized by collapse and convulsions. The respiratory centers are depressed. The respiratory movements are shallow and infrequent. The convulsive, vagus, vasomotor and pupillo-dilator centers are stimulated. The extremities and the muscles of the face and neck twitch convulsively; there are gasping movements; the body is rigid and arched backward. Urine and feces are expelled. The pulse is slow and soft, at first strong, then progressively weaker. The pupils are at first constricted, then widely dilated until death. The heart continues to beat weakly for several minutes after the respiration has stopped. Artificial respiration during this interval generally results in recovery. *Death* occurs within six or eight minutes, if the trachea is tied. The *autopsy* shows the veins of the upper part of the body and the right heart greatly distended with very dark blood. *If the asphyxia is produced slowly,* the first symptoms are cyanosis and dyspnea on exertion. The individual becomes stupefied, but so gradually that he may not be aware of his condition. The stupor passes into unconsciousness and this into collapse. The motor symptoms may be entirely absent.

The **effects of stale air** are not due to oxygen deficiency or even to carbon dioxide excess. "Pure" air contains 0.03 per cent of CO_2; in badly ventilated rooms it may reach 0.3 per cent, which is far below the effective concentration. Human expired air contains small amounts of toxic substances, presumably volatile bases, which depress the frog heart (Gramenitzky and Siwerzew, 1935); but it is questionable whether their quantity is significant. The acute discomfort and the suffocating sensation experienced in these places is largely psychic, attributable to the heat, humidity, odors, noise, and so on. Whether this accounts also for the severely detrimental effect on health and resistance, the increased tendency to tuberculosis, and so forth, which are associated with habitually deficient ventilation, is an open question. Continued or repeated exposure to gases—particularly those acting upon the blood, and indeed to any poison which alters the blood, such as acetanilidid—does not generally cause tolerance, but increase of susceptibility.

Indifferent gases, nitrogen, hydrogen; the "rare gases," helium, argon, and the like, act merely as diluents of oxygen and produce quantitatively the effects described under oxygen deficiency. One volume of such gases may be added to two volumes of air (reducing the oxygen percentage to 14) before any symptoms set in. Equal volumes are dangerous. They interfere with efforts to escape. Three volumes to one of air is quickly fatal. The *rare gases* are not essential to life: continuous sojourn of mice in an artificial air of pure oxygen and nitrogen for over forty days produced no symptoms or lesions whatsoever (Barach, 1934).

Helium as Therapeutic Diluent of Oxygen.—Because of its low density, a mixture of 21 vol. of oxygen and 79 vol. of helium can be moved through small orifices with half the effort required for air. This is practically unimportant with the normal airway, but is effective for relieving obstructive dyspnea, especially in prolonged asthmatic attacks when epinephrine has failed (A. L. Barach, 1936); and in postoperative tracheal edema, hemorrhage and laryngospasm (Eversole, 1938). Its actual value in bronchiolar obstruction is not great.

Helium, U.S.P., is a colorless and odorless gas, very slightly soluble in water.

The **treatment of asphyxia** should be directed primarily to the oxygen deficiency. The patient should be removed to fresh air, but protected against cold, as the temperature control is impaired. He should be laid flat and prone, with the face turned to one side. Oxygen should be administered, preferably with 5 per cent of carbon dioxide (Y. Henderson), to increase the pulmonary ventilation. This also helps to restore the circulation and to offset the cerebral depression (Gellhorn, 1936). If the patient has stopped breathing, artificial respiration should be started at once and kept up for fifteen to thirty minutes. This is not likely to be injurious; even positive and negative pressure resuscitating machines, used on anesthetized and curarized dogs for one to three hours, gave no evidence of lung damage (H. Schwerma and Ivy, 1945). After recovering, the patient should be kept warm, to prevent pneumonia. Alcohol is contraindicated (Henderson and Haggard). The treatment must be started promptly. Success cannot be expected if the respiration has stopped for fifteen minutes (B. D. Ross, 1945). The heart beats at most ten minutes, more often only six minutes, after the respiration stops, and death occurs in ninety to 120 seconds after complete arrest of the heart. Resuscitation is unsuccessful or incomplete after seven to ten minutes of complete cerebral anemia (G. N. Stewart and Pike).

The heart has been restored clinically by direct cardiac massage after it has been arrested ten or eleven minutes. The brain stem resumed function, but the patient remained in coma for twenty-six days, when death occurred from pneumonia and urinary imfection. Autopsy showed degeneration of the cerebral and basal ganglia and cerebral cortex (Howkins *et al.*, 1946).

OXYGEN THERAPY

The administration of oxygen is useful only in those forms of asphyxia in which the access of oxygen to the blood is hindered, as by *vitiated air* (anesthesia, mines, wells, and the like); by *mechanical interference with respiration* (suffocation, drowning, croup, and so on); by *depressed respiration* (anesthesia, collapse); or by a *diminished absorbing surface of the lung* (pulmonary edema, pneumonia); and in carbon monoxide poisoning. Higher concentrations, up to 100 per cent, give prompter relief, and are safe for some hours, but should be reduced to 60 per cent if this gives sufficient saturation of the blood, as it is of little benefit unless its concentration in the air actually inhaled is at least 60 per cent, three times that of ordinary air. Concentrations above this may become injurious if inhaled longer than twelve hours. Its benefits cease within a few minutes after its inhalation is discontinued, so that it must be administered continuously as long as the need for it exists. At high altitudes, undiluted oxygen may be inhaled indefinitely since its pressure is lowered.

Pneumonia responds to continuous oxygen inhalation with marked symptomatic improvement, especially postoperative cases in which the virulence of the infection is generally less. In the oxygen chamber, the patients often show a crisis-like drop of 2° to 5° F. in the febrile temperature, with corresponding decrease of the rate of the heart and respiration. The administration must be continued as long as needed, and must be resumed if its discontinuance is followed by a temperature rise of more than 1° F.

In *pulmonary edema from irritant gases*, the gas exchange in the lung is hindered by the alveolar and bronchial foam. The inhalation of oxygen converts this into an oxygen foam and relieves the cyanosis (Haldane, 1918). It does not, however, help to remove the accumulation of carbon dioxide, so that the air hunger persists (C. F. Hoover, 1918).

According to Haldane, 1918, oxygen inhalation is of considerable benefit in *emphysema* and gives temporary relief in *asthma*, but has little effect on the dyspnea of *cardiac disease* or of nephritis. *Coronary thrombosis* has been reported benefited by oxygen therapy (Barach and Levy, 1934), but animal experiments indicate that it is useless (Wiggers). In *anemia* (whether from hemorrhage or any other cause, such as chlorosis or leukemia) asphyxial conditions result, not from deficient supply of oxygen, but from a deficiency of hemoglobin. The inhalation of oxygen, in these cases, does not increase the quantity of oxygen carried by the hemoglobin, but that carried in solution by the plasma. The practical benefits are not great. Indeed, *in chronic cyanosis generally, oxygen administration is not advisable*, as it tends to interfere with compensation. *In epilepsy*, the number of seizures is reported to be decreased by oxygen administration and to be increased by oxygen deficiency (W. G. Lennox and Behnke, 1936).

Inflammation.—Mustard conjunctivitis is checked by the intravenous injection of substances containing chemically active oxygen, such as iodosobenzoic acid. Conversely, inflammation is intensified by cyanides, which heck oxidation (Amberg *et al.*, 1917).

Administration.—In acute anoxemia the oxygen may be administered undiluted, through a valved mask or pharyngeal or tracheal catheter, after passing the compressed gas from the tank through warm water. Continuous administration is necessary because the oxygen is used immediately and not stored, and temporary anoxemia on withdrawal produces sharper reactions than when the functions have adjusted themselves as well as may be to a given level of oxygen content. This close and continuous control of the oxygen content is practical only in an oxygen chamber or tent. The amount must be controlled by air analysis three or four times daily. The carbon dioxide is kept between 1 and 1.5 per cent, by circulation through alkali, for the respiratory stimulation of higher concentrations fatigues the patient without improving the oxygenation (D. J. Cohn *et al.*, 1939). The fire and explosion danger of oxygen must be remembered. Oil must not be used in the valves.

Intravenous injection of oxygen was described by Tunnicliffe and Stebbing, 1916. It gives rapid relief to the cyanosis and dyspnea. In man, the gas can be injected into a vein at the rate of 600 to 1200 cc. per hour, usually beginning with the rate of 500. The heart must be watched, and the injection stopped if any irregularity appears. Unless great care is used, intravenous injection of oxygen is more likely to accentuate anoxemia, presumably by producing pulmonary gas emboli and cardiac insufficiency (Bourne and Smith, 1927).

Subcutaneous injection of oxygen was introduced by Derose, 1912. McCrae, 1914, believed that it has a limited field as substitute for inhalation. Y. Henderson, 1918, stated that life may be maintained by *intraperitoneal* injection of oxygen. *Oxygen absorption from the skin* occurs to some extent (Shaw, Messer and Weiss, 1929), sufficiently to prevent local cyanosis between two ligatures of the arm, if this is immersed in oxygen (Goldschmidt and McGlone, 1932).

Oxygen, U.S.P. (*Oxygenium*), 99 per cent by vol.

CARBON MONOXIDE

Carbon monoxide (carbonic oxide, CO) has great toxicologic importance, through its occurrence in artificial illuminating gas, especially "water gas" (not in "natural gas") and as a product of incomplete combustion. It is a colorless, odorless and nonirritant gas, so that there is no warning of its presence. It forms a relatively firm compound with hemoglobin, thereby preventing it from carrying oxygen, and thus produces asphyxia. This agrees with ordinary asphyxia, except that the skin and mucous membranes are usually not cyanotic, but are often bright red, owing to the color of CO-hemoglobin. High concentrations depress various vital activities directly, but this depression does not play a significant role in ordinary poisoning.

Historical.—Claude Bernard made an important study of carbon monoxide poisoning (Leçons sur les Anesthétiques et sur l'Asphyxie, 1875) and showed that it does not act directly, but by combining with hemoglobin. He advised treatment with artificial respiration, preferably with oxygen, and transfusion. Good reviews of carbon monoxide poisoning are given in Henderson and Haggard's "Noxious Gases," and by E.M.Killick, 1940.

The **frequent incidence of carbon monoxide poisoning** is partly suicidal, partly accidental. *Accidental* deaths occur chiefly through defective ventilation of rooms where the gas is formed by incomplete combustion, in stoves, damped furnaces, automobile motors, in conflagrations and in mine explosions. These also furnish occasion for chronic poisoning. Carbon monoxide does not occur spontaneously in nature, aside from these conditions. The easy accessibility of the gas, in illuminating gas and automobile exhaust gas, and the easy exitus, explains why it is used in over half of all *suicides* by poisons. The recorded suicides by carbon monoxide in the United States number over 5000 annually, and the actual number is doubtless higher. In New York City, carbon monoxide is responsible for three-fourths of the cases of suicidal poisoning, two-thirds of the accidental and four-fifths of the homicidal (Helpern, 1939).

Occurrence in Artificial Illuminating Gas.—Carbonic oxide constitutes 4 to 10 per cent of ordinary *coal gas* and 30 to 40 per cent of *water gas*. Blast furnace gas contains 24 to 30 per cent, producer gas 22 to 26 per cent. It is the principal toxic ingredient of these gases, but does not account fully for the toxicity of coal gas (A. H. Huebner, 1916). The difference is due to coal tar products (which may be removed by passing the gas through oil). The disagreeable odor of gas is due to sulfur compounds. These are not toxic, but serve as warning of the escape of gas. They are removed by filtration through soil, so that underground breaks in gas mains are especially dangerous. *Automobile exhaust gases* contain an average of 6 per cent of CO, roughly 1.4 liters per minute per horsepower. The engine of a small automobile when running in a small closed garage would contaminate the air to a dangerous degree in about three minutes and be fatal within five minutes (U.S.P.H.S.).

Manner of Action.—In the concentrations reached in intact animals, carbon monoxide acts only by displacing oxygen and has no direct action of any kind; for if an animal is made to breathe oxygen under 2 atmospheres pressure (which renders it independent of the hemoglobin), the addition of carbonic oxide in any amount produces no symptoms.

Action on Hemoglobin.—Carbon monoxide forms a firm compound, carbonic oxide hemoglobin, with the blood pigment. Its spectrum differs but slightly from that of oxyhemoglobin, but it is not reduced by ammonium sulfide (Hoppe-Seyler, 1864, 1865). It has a cherry red color (Piorry, 1826), quite different from that of oxyhemoglobin, especially when it is diluted. This forms one of the best tests for its presence. The ochre tint can also be distinguished microscopically in the corpuscles after poisoning (Bernard).

The scarlet color of the blood is observable at *necropsy*, and the CO bands have been demonstrated six weeks after death (Wachholz and Lemberger, 1905). With survival, they have been present for ninety-six hours. In some parts of the body the blood may appear black, presumably when death occurred before the CO was uniformly distributed; but even the black blood gives the CO-hemoglobin spectrum. The cadaveric ecchymoses have a rose color (Brouardel, Les Asphyxies; he suggested its use to preserve the red color in anatomical specimens).

The CO behaves toward hemoglobin essentially as if it were an isotope of oxygen (E. T. Adams, 1934), but with a relative affinity about three hundred times greater. The reaction with hemoglobin may be represented as $HbO_2+CO \rightleftarrows HbCO+O_2$. With the CO in the atmosphere of $\frac{1}{300}$ that of oxygen, *i. e.*, at 0.07 per cent by volume, half of the hemoglobin would be transformed to carbon monoxide hemoglobin.

In the absence of oxygen, the combination of hemoglobin with CO_2, and the dissociation of carboxyhemoglobin, follow the same laws as those of oxyhemoglobin, but the reaction with carbonic oxide is much slower than with oxygen, in combining but especially in releasing; under body conditions about a tenth as fast in combining, about a sixtieth as fast in dissociation (Roughton, 1934). This slow release accounts largely for the greater "affinity" of carbonic oxide hemoglobin. Light, temperature and *p*H affect the combination and dissociation in different degrees; light lowers the equilibrium content, (*K*) by accelerating the dissociation of HbCO; increase of temperature also lowers (*K*) (Hartridge, 1912). It is not altered by barometric pressure (J. L. Lilienthal, Riley *et al.*, 1946). The (*K*) is practically independent of salt content, laking or purification of the hemoglobin (F. J. W. Roughton, 1934), but it varies considerably for different animals. At 15° C., it is 570 for dogs' hemoglobin, 120 for rabbits'. The affinity of *myohemoglobin* for carbon monoxide is much less than that of blood hemoglobin (review, E. M. Killick, 1940). Increase of the CO_2 in the blood decreases the affinity of hemoglobin for CO relative to O_2, so that hypercapnia tends to more rapid elimination of carbon monoxide (Stadie and Martin, 1925).

Fate.—The *absorption* and excretion of carbon monoxide occur exclusively through the lungs, as it is but little soluble in water (0.0178 per cent by volume at 40° C.). It is not absorbed through the human skin (Schütze, 1927) and does not penetrate through the skin of rabbits, while CO_2 and NH_3 do so readily (E. Burgi, 1936). The *CO is excreted* (*unchanged*); practically none is oxidized to CO_2. It may penetrate post mortem into a cadaver, but so slowly that it cannot be demonstrated in the internal organs (Stoll, 1909). Claude Bernard observed that CO delays the postmortem degeneration of blood corpuscles, the serum separating very clear. Oxidation of CO in tissues is less than 0.1 per cent (Gregersen, 1945; isotope). *In vitro*, skeletal and heart muscle may consume up to three times as much oxygen, in a mixture of 79 per cent CO and 21 per cent oxygen, as in ordinary air; but other tissues show little increase (Carleton and Fenn, 1938). The oxidation of CO in frog skeletal muscle is accomplished by a distinct enzyme system, which is inhibited by cyanide, azide and hydroxylamine. The *cytochrome oxidase* system is inhibited by CO in many cases (J. N. Stannard, 1940). With yeast and germinating seedlings the effects on oxygen consumption and CO_2 production appear more complex (Tang, 1932).

After mild CO poisoning in man, about 90 per cent of the inhaled CO is eliminated by the lungs in the first four hours; but during the first hour the expired air contains only 60 to 70 per cent of the CO that leaves the blood. The remainder is probably held temporarily by the hemoglobin pigments outside the blood stream (Roughton and Root, 1945).

Course of Carbon Monoxide Poisoning.—The phenomena agree with those of ordinary asphyxia, except that cyanosis may be absent; the skin is pink or pale, and the lips are bright red, the color of CO hemoglobin. This is of diagnostic importance. The effects are insidious, the person becoming unconscious often with no premonitory symptoms, "the patient gliding imperceptibly from waking to sleep and from sleep to death." The clinical cases may be classified as acute, relapsing and chronic (McConnell and Spiller, 1912). The *symptoms of acute illuminating gas poisoning* generally begin with a feeling of discomfort, throbbing blood vessels; dizziness, headache, weakness and sometimes nausea and vomiting; sometimes pain in the extremities and muscular twitching. The temperature is normal, the pulse full and bounding, the blood pressure elevated; feeling of constricted thorax; pupils widely dilated; gradual drowsiness, stupor and *unconsciousness*. After this has set in, the respiration becomes accelerated and stertorous; the skin dusky, often with a diffuse reddish coloration, or pink patches, sometimes with blisters. Reflexes are lost; involuntary evacuations of urine and feces are exceptional. Tetaniform convulsions may occur and be followed by marked muscular rigidity, especially in the jaws. The convulsions are produced only in very rapid poisoning, however, and are therefore rare clinically. The pulse and respiration gradually weaken, ending in apnea, and finally arrest of the heart. Death sometimes occurs acutely through aspiration of vomited matter during unconsciousness. *Recovery* is often slow, but it may occur even when the coma has lasted two or three days. Convalescence is also often tardy, with pulmonary and nervous sequels. Patients who recover consciousness under treatment suffer for several days from headache and dizziness, perhaps with some gastric distress, due to cerebral edema (H. S. Forbes *et al.*, 1924). *Different sources of CO* may introduce impurities which modify the effects. The coma is longer and more severe in illuminating gas poisoning than with pure CO (Y. Henderson and Haggard, 1918, 1922). In automoblie gas, the benzene vapors play a minor part.

Individual Functions in Acute Poisoning.—Carbon monoxide produces progressive fall of *blood pressure*, and marked slowing of the *heart*, apparently not affected by section of the vagi. The *respiration* is at first slow and shallow, then slower and deep (D. E. Jackson and Chance, 1925). If the carbon monoxide is diluted with nitrogen instead of oxygen, the blood pressure rises (Brewer, 1937). *Heat regulation* is disturbed and the temperature may either fall or rise. *Protein metabolism* is markedly increased, even in relatively mild poisoning, probably by a central action. The nitrogen excretion may reach three to four times the normal level and remain high for one or two weeks. *Glycosuria* by mobilization of hepatic glycogen occurs in one-twelfth to one-third of the patients. It is relatively mild and short, generally not longer than a day (H. Jacoby, 1930). *Albuminuria* indicative of nephrosis occurs in about the same ratio; as also urobilinogen, showing some hepatic insufficiency. The *necropsy findings* in sixty-three deaths from garage poisoning, reviewed by McNally, 1928, revealed small hemorrhages in many organs, including the brain. The brains of animals killed acutely with carbon monoxide are edematous and markedly congested with severe perivascular perineuronal edema, most marked in the corpus striatum, cortex and dorsal motor nucleus of the vagus. The vessels throughout are dilated and packed with red cells, with a few petechial hemorrhages. The lesions in slow poisoning, with eight to fifteen hours' exposure to 0.2 per cent, differ only in degree (Sayers *et al.*, 1934). Bilateral softening of the globus pallidus occurs in almost every case of acute asphyxia in which coma has lasted longer than twenty-four hours (Helpern, 1939).

Direct Actions on Isolated Organs and on Lower Organisms.—Tadpoles are not injured by saturating the water with CO. Intact *frogs* lose their *reflexes* in pure CO after about two hours, about the same as in hydrogen (Kochmann, 1920). If the vessels were perfused with saline to remove all hemoglobin, exposure to CO abolishes the remaining reflexes, indicating direct depression of the central nervous system (Fallori, 1932). It also depresses the exposed cerebrospinal axis (Baglioni preparation) of the toad (Mitolo, 1929, 1931). The isolated heart (Straub preparation) is not materially injured by pure CO (Kochmann). The conductivity and excitability of *nerve trunks* is depressed reversibly, as in nitrogen. The direct excitability of skeletal *muscle* is greatly diminished by dilute CO, and recovery requires long aeration (F. Krause, 1930). It may be assumed that the CO binds the myohemoglobin. *Infusoria* and *ciliated epithelium* are checked, but not killed. The growth of *bacterial* cultures is slightly retarded. The germination of the seeds of higher plants is not affected. The gas kills plants when applied to the leaves, but not when applied to the roots (Heider, 1914). Oxidation in insects and plants is retarded (Haldane, 1927).

Relation of CO Concentration and Effects.—The effects of carbon monoxide depend upon the amount of hemoglobin which it binds and withdraws as oxygen carrier. This can be calculated from the carbon monoxide tension of the air; but the element of time also enters, to allow for the dead space of the air passages and for absorption of adequate quantities, especially with dilute mixtures (Gréhant).

Air containing 0.07 volume per cent of CO (7:10,000) is capable of converting 50 per cent of hemoglobin into carbon monoxide hemoglobin. *In vitro*, this is accomplished instantly; but several hours of inhalation would be necessary to approach this result for a man, for only 210 cc. of CO would be inhaled in an hour. If this were all absorbed and bound by hemoglobin, it would suffice to saturate only a fifth of the hemoglobin, instead of a half. In fact, however, only about half of the carbon monoxide is absorbed during the early stages of exposure. Anything which increases respiration, such as severe muscular work, increases the rapidity with which equilibrium is attained. In man at rest, half of the final saturation is reached in about forty-seven minutes; twice as rapidly if walking; three times, with fairly hard work. Small individuals approach saturation more rapidly, because the volume of the respiration varies with the body surface (in rest), while the volume of the blood varies with the weight. For a given concentration the time till unconsciousness is about twenty times as long for man as for a mouse or canary. The *elimination* varies in the reverse direction. About a third of the absorbed gas is eliminated in two hours after the exposure has been discontinued; the remainder much more slowly (Killick).

For ordinary conditions, Henderson and Haggard propose a *toxicity factor* obtained by multiplying the concentration of CO in the air (volume per 10,000 or cubic centimeter in 10 liters) by the time in hours. If this factor is below 5, there are no acute symptoms. The effects begin to be perceptible with 6, as slight headache and inertia. With 9, the headache is severe, with nausea. With 15 to 20, there is serious danger; 40 or more per 10,000 is fatal in less than an hour.

The following tabulation, chiefly from data of Sayers *et al.*, gives the *actual ranges of the degree of hemoglobin saturation in man* at rest:

CO in Air, Parts per 10,000	Hours of Exposure	Percent of Hemoglobin Bound by CO	
		Under These Conditions	At Complete Equilibrium
1 to 2	5 to 6	1 to 20	13 to 23
3	4 to 5	22 to 27	33
4	1	15 to 19	38
4	2	21 to 23	
	With Exercise		
2.5	1	14 to 16	
3.3 to 3.6	1	17	
4	1	23	

The *correspondence of the effects with the percentage of hemoglobin saturation* is as follows (McNally, 1928; Dreser, 1891; Balthazard and Nicloux, 1911): 0 to 10 per cent: no symptoms. 10 to 20 per cent: tightness across forehead, possibly some headache; flushed skin; yawning. 20 to 30 per cent: headache, throbbing temples; dizziness and palpitation on exertion. 30 to 40 per cent: severe headache, weakness; dizziness, dim vision, nausea, emesis. 40 to 50 per cent; as above, plus increased respiration and pulse rate, coma; intermittent convulsions; Cheyne-Stokes respiration. 60 to 70 per cent: as above, plus weakened heart and respiration; possibly death. 70 to 80 per cent: weak pulse, slow respiration; respiratory failure; death. 90 per cent: prompt cardiac arrest. The limit of safety is 18 to 20 per cent (Dreesen and Sievers, 1946).

Toxic Concentrations in the Air.—Gruber, 1881, found that 0.024 per cent is harmless even after several hours. The toxicity begins with about 0.05 per cent, is severe with 0.07 per cent, and dangerous with 0.16 per cent; 0.2 to 0.4 per cent is generally fatal. A man at rest would collapse within an hour when exposed to 0.2 per cent (Burrell and Gauger, 1919). Several persons in the same room may be affected in different degrees, owing partly to air currents (the gas is slightly lighter than air: sp. g., 0.967), partly to differences in the absorption velocity.

Newborn rats and rabbits have relatively high resistance, which declines by successive steps for two or three weeks, when it becomes stable. Newborn guinea pigs do not show this resistance, presumably because they are more mature (J. A. Cameron, 1941). *Fetal blood* may contain so much less CO than that of the mother (Quinquaud and Gréhant) that cesarean section may be indicated to save a fetus near term.

Sequels.—The severe and prolonged anoxia which is liable to occur in carbon monoxide poisoning may cause cellular disorganization, functional and organic, the latter persistent or permanent. The direct anoxic damage is complicated by the effects of capillary injury, especially in the lungs, skin and central nervous system, with edema and small hemorrhages, followed by perivascular infiltration and focal necrosis.

The principal sequels are: aspiration pneumonia, often fatal; palpitation, localized hyperemias, gastro-intestinal disturbances, transient asphyxial glycosuria (review, S. Weber, 1904), cutaneous eruptions, herpes and vesication, localized edemas, gangrene (J. E. Briggs, 1919). Nervous symptoms of central and peripheral origin may develop some weeks after apparent complete recovery ("*relapsing type*"). The *pneumonia* may set in after one or two days, or more quickly in serious cases by the confluence of localized bronchopneumonic patches and lead to death in a few days. The temperature may rise excessively high, presumably because the heat centers are injured. *Myocardial damage* may develop slowly, with the same pathologic foundation as in the brain and other organs. These have also been produced in animals. Coronary thrombosis is frequent (H. G. Beck and Suter, 1938). *Polycythemia* may occur promptly or progress slowly through several months and last for years. It has been attributed to damage of the basal ganglia.

Nervous and mental changes are serious and persistent only in severe cases of profound and lasting anoxemia, when resuscitation was difficult and coma prolonged. They do not occur from chronic exposure to low concentrations.

In a study of forty-three patients with persistent mental nervous sequels, Shillito *et al.*, 1936, found that in two-thirds the symptoms had started immediately after the poisoning; in the other third a clear period of seven to twenty days had intervened. About half of the patients eventually recovered. The *mental sequels* were chiefly confusion psychosis with disorientation, lack of judgment, and amnesia. Aphasia was much less common. Hallucinations, delusions and convulsions were not conspicuous. Nervous symptoms ranged from slightly increased deep reflexes to well advanced Parkinsonian syndrome, attributed to degeneration of ischemic areas in the thalamic region and basal ganglia. Some patients develop sensory disturbances (violent headache, lancinating pains in the extremities) and peripheral motor neuritis. Rutenburg, 1939, reported *nystagmus* and *deafness* from injury of the eighth nerve, appearing in twenty-four to forty-eight hours in actute poisoning, and also in chronic poisoning.

Chronic exposure to carbon monoxide occurs industrially and in the daily life of cities. The effects are those of anoxemia. Some acclimatization occurs by habitual exposure to low concentrations (Killick, 1937), chiefly through polycythemia, and by adaptation of the circulation; but the general health is likely to suffer (H. G. Beck, 1936).

The *clinical symptoms* are headache, naüsea, vertigo, weakness, anemia, slowed intellect and failure of memory, and all the phenomena of the acute type more slowly developed. The memory for recent events is impaired much more than for those of older standing (S. Brown, 1906). The nervous phenomena have been referred to serous leptomeningitis ((Zieler, 1897). Slow CO poisoning shows marked histological disintegration of tissues, extreme hepatic congestion and atrophy of the liver cells, attributed to cardiac failure (J. A. Campbell, 1929). The symptoms of chronic poisoning occur with 4 per cent saturation of the blood, and continued exposure to 1:20,000 air may therefore be considered injurious (E. Kohn-Abrest, 1927). Exposure of dogs to 0.01 per cent for five and one quarter hours daily produces electrocardiogram changes, degeneration of cardiac muscle, and damage in the cerebral and cortex and basal ganglia (F. H. Lewey and Drabkin, 1944).

Acclimatization.—Men exposed repeatedly to low concentrations develop considerable tolerance as regards symptoms, but without change in the hemoglobin content or cell count. Somewhat higher concentrations, 0.01 to 0.05 per cent for several hours daily for several months, gradually induce hypersusceptibility and neurasthenic symptoms (Killick). *Guinea pigs* can be accustomed to live for months in an atmosphere by which 25 per cent of their hemoglobin is saturated with CO. This tolerance is attained by an increase of the corpuscles and hemoglobin, so that the oxygen capacity becomes almost normal. *Rats* exposed to ⅓ per cent CO for an hour daily for 150 consecutive days lost weight and became unkempt. The hemoglobin percentage and the cell:plasma ratio rose and remained high, with considerably increased tolerance (acclimatization). Both sexes, however, became sterile, the males much earlier than the females (I. R. Williams and Smith, 1935). Mice exposed to the same concentration also developed infertility and cardiac hypertrophy (J. A. Campbell, 1934). Dogs and guinea pigs react with falling of hair, salivation, temporary fall of temperature. The hemoglobin rises slightly in dogs (H. Fetzer and Weiland, 1934).

Incidental CO concentration in city air arises chiefly from automobile traffic. The air in half of the cars examined at random on highways contained measurable traces, and 7 per cent of the cars had "dangerous concentrations" (L. T. White, 1934). R. F. Sievers *et al.*, 1942, found that the air in the Hudson Tunnels averages 0.007 per cent. Traffic officers on duty there for thirteen years showed no ill effects. Their CO hemoglobin ranged from 0.5 to 13 per cent. Gettler and Mattice, 1933, found the hemoglobin bound by CO in the blood of persons living in rural localities less than 1 per cent; in persons living in New York City under conditions of minimal exposure, it was 1 to 1.5 per cent; in street cleaners it rose to 3 per cent; and in two taxicab drivers it was 8 and 19 per cent. Tobacco smoking may also increase the CO of the blood somewhat (to 3 or 10 per cent, Dreesen and Sievers, 1946), but none of the smokers in the rural group had over 0.64 per cent. CO is alone concerned in the chronic effects of automobile exhaust gas (Supfle and May, 1934).

Treatment of CO and illuminating-gas poisoning is usually successful if begun while the heart is beating. In the presence of a large excess of oxygen, the carbonic oxide hemoglobin is again decomposed, and the CO eliminated (not burned). The treatment therefore consists in artificial respiration or, better, the inhalation of oxygen containing 5 or 10 per cent of CO_2, the latter being more efficient (D. C. Walton *et al.*, 1926). Epinephrine may be injected (½ to 1 cc. of 1:1000) to contract the spleen and so mobilize its unpoisoned corpuscles. Bleeding with transfusion of healthy blood is effective (Claude Bernard; Worm-Mueller; Crile and Lenhart, 1907). Patients should not be exposed to cold. With respiration, natural or artificial, of ordinary air, the CO-hemoglobin is decomposed below the danger limit within an hour, the CO being practically eliminated in two or three hours. It is therefore superfluous to use oxygen or transfusion after an hour. If the coma continues longer than an hour, it is due to persisting injury of the nerve centers by the early asphyxia. Once this injury has occurred it would not be helped by oxygen. The existence of acidosis indicates alkalis; otherwise the late treatment would be expectant (J. E. Nadler *et al.*, 1934). The *prognosis* varies with the duration of the exposure and of the coma. It is bad if the coma has lasted more than forty-eight hours, of if edema or cutaneous blebs have developed (G. I. Jones, 1909). Even in favorable cases, recovery is rather more slow than with most gases; but the acute effects have generally disappeared within three hours.

The displacement of CO by oxygen is rather slow. (In a case of industrial poisoning with 40 per cent COHb saturation, this was reduced to 25 per cent after an hour of oxygen administration; to 8 per cent in four hours; and traces were still present after twenty-four hours; Nicloux and Herson.)

Methylene blue injection as an antidote to carbon monoxide poisoning has been advocated especially by M. M. Brooks, 1933 (50 cc. of 1 per cent, intravenously), with the expectation that it would supply oxygen to the tissues directly. She also reported that it changes CO-hemoglobin into oxyhemoglobin; but others claim that it forms methemoglobin and would do more harm than good (Haggard and Greenberg, 1933). Mack and Smith, 1933, found that it had no effect on the survival of CO poisoned cats, in either direction.

OXYGEN CONVEYANCE BY HEMOGLOBIN

The ability to combine loosely with oxygen, so that this is readily released, is a peculiar and most essential property of hemoglobin, although this has other important functions in neutrality regulation, as an amphoteric protein, acting as a weak acid buffer and as a base for the transport of carbon dioxide, with which it forms an alkaline bicarbonate. It does not bind CO_2 directly in the sense that it binds oxygen or carbon monoxide.

Chemical Structure.—Hemoglobin consists of a characteristic colored iron compound, *hemin*, and a colorless protein, globin. These can be separated and may recombine under certain conditions (Robert Hill). The globin may be replaced by much simpler bases, such as pyridine or nicotine, yielding *hemopyridine* or *hemo-*

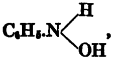
nicotine. They react with oxygen similarly to hemoglobin. *Hemin* (Teichmann, 1853) is a relatively simple tetrapyrrole compound containing four atoms of ferrous iron bound to the pyrrole nitrogen. The iron is its active nucleus, and the biologically important reactions of hemin are reactions of complex iron compounds (O. Warburg, review, 1928).

Reaction with Oxygen.—The iron of the hemoglobin reacts reversibly with molecular oxygen, one molecule of oxygen for each atom of iron, to form oxyhemoglobin: $Hb + O_2 \rightleftarrows HbO_2$. It is not known whether the O_2 links directly to the Fe^{++}, but the ferrous is not oxidized to ferric iron. Oxyhemoglobin is a true stoichiometric chemical compound, but the union is loose and can be dissociated by relatively simple conditions, such as change ofp artial pressure of oxygen or of *p*H. Oxyhemoglobin is more acid than hemoglobin (Haldane), so that the saturation curve is not in simple or exponential proportion of the oxygen pressure, but sigmoid. This aids in expelling CO_2 in the lungs. Fetal hemoglobin is reported to have a greater affinity for oxygen than that of adults (Barcroft, 1936), attributed to differences in the globin fraction. Normally, saturated oxyhemoglobin carries about 1.36 cc. of O_2 per Gm. This may be replaced by the same volume of CO (D. B. Morrison and Hisey, 1935). Normal blood at complete (100 per cent) saturation carries 18 to 20 cc. of oxygen per 100 cc. of blood. The saturation is practically complete (ca. 97 per cent) in arterial blood in the body, or *in vitro* with 15 per cent of oxygen in the air. Reducing the oxygen of the air to 9 per cent reduces the hemoglobin saturation to 90 per cent. Mixed venous blood has about 75 per cent saturation; with vigorous work this may fall to 40 per cent or even less. Carbon dioxide or lowered *p*H decreases the oxygen-combining power of hemoglobin.

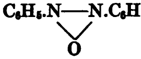
The **reaction of hemoglobin with carbon monoxide** appears analogous to that with oxygen, the distribution being determined by the partial gas pressure: $\frac{Hb.O_2}{Hb.CO} \times \frac{CO}{O_2} = K$.

Other Molecular Hemoglobin Compounds.—The nature of these is less understood. There is a nitric oxide hemoglobin, HbNO, of a cherry-red color (also a NO methemoglobin), and a sulfhemoglobin, possibly HbH_2S, but the mode of combining may be quite different. It is doubtful whether these can be formed in the body under normal conditions.

Methemoglobin is formed quite differently, by the oxidation of the bivalent (ferrous) iron of hemoglobin into the trivalent (ferric) iron, which cannot carry molecular oxygen: $HbFe_2''O_2 \rightarrow HbFe'''OH$. This may again be reduced to oxyhemoglobin, but only slowly. The oxidation to methemoglobin can be accomplished *in vitro* by oxidizing agents, such as ozone, peroxides, chlorates, quinone, ferricyanide. Of these, only chlorate is effective in living animals, but methemoglobin is formed in life by various agents that are not directly oxidizing; for instance, by *aniline* and nitrobenzene (von Issekutz, 1939). Both form *phenylhydroxylamine*,



$C_6H_5.N\begin{smallmatrix}H\\OH\end{smallmatrix}$, which oxidizes to azoxybenzene,



$C_6H_5.N\underset{O}{—}N.C_6H_5$. Oxygen is liberated in this reaction and forms methemoglobin. *Paraminophenol* is also formed from aniline and nitrobenzene, and part of this undergoes transformations, probably by way of *quinonimine,* which liberate active oxygen and therefore form methemoglobin. As this restores the reagent, it acts as a catalyzer, so that a small quantity may form a large amount of methemoglobin. *Nitrites* also form methemoglobin in the living animal. In rabbits, 0.15 Gm. of $NaNO_2$ per Kg. converts 15 per cent of the hemoglobin into methemoglobin. *Dextrose* injection (1 to 2 cc. of 1 per cent per Kg.) is reported to convert this back into hemoglobin, within five minutes. It acts similarly *in vitro* (M. M. Brooks, 1934). However, W. W. Cox and Wendel, 1941, report that variations in the dextrose concentration from 50 to 250 mg. per 100 cc. have no effect on the rate of methemoglobin formation, in animals or *in vitro*. *Methylene blue* acts in both directions, forming methemoglobin from oxyhemoglobin, and oxyhemoglobin from methemoglobin. It speeds greatly the reduction of methemoglobin by ascorbic acid (C. S. Vestling, 1942).

Methemoglobin tends to revert to hemoglobin at the rate of about 12 per cent per hour *in vivo* or *vitro* (Cox and Wendel, 1941). Many substances that form methemoglobin also form disintegration products, "*verdohemochromogens,*" intermediate to bilirubin. These have been mistaken for sulfhemoglobin, which often accompanies them (F. Jung, 1939).

The *physiologic significance of methemoglobin formation* rests on inability to carry out the functions of oxyhemoglobin. This produces asphyxia of the tissues. Its presence also interferes with the release of oxygen by oxyhemoglobin (R. C. Darling and Roughton, 1942). Normal blood, however, contains a small amount of methemoglobin, 0.01 to 0.5 Gm. per cent (W. D. Paul and Kemp, 1944); and pure methemoglobin solutions may be injected into the blood, without causing any symptoms in normal dogs. In acidotic dogs it produces renal injury, hydropic degeneration in the proximal and necrosis in the distal convoluted tubules (Bing, 1944). The half-life of methemoglobin in the circulating plasma is about eight hours, and practically all has disappeared in three days. Much is converted into oxyhemoglobin, about a third is excreted as such or as oxyhemoglobin into the urine (Van Slyke, 1945), part is secreted by the bile; the remainder goes to the hematopoietic organs. The restoration of oxyhemoglobin from methemoglobin is considerably slower than from carbonic oxide hemoglobin, and the effects are correspondingly more lasting. They are considerably less dangerous, however, than those of carbon monoxide. Dogs injected with sodium nitrate became unconscious when 80 per cent of the hemoglobin is changed to methemoglobin; cats exposed to carbon monoxide became unconscious when the CO hemoglobin reached 60 per cent, and died at 71 per cent (D. Lester and Greenberg, 1944). The conversion of a third of the hemoglobin into methemoglobin causes only slight symptoms; life is still possible when three-fifths of the hemoglobin has been replaced. Life becomes extinct when the hemoglobin has sunk to one-third. The condition becomes dangerous only if the methemoglobin former continues its action. This does not occur with therapeutic doses of any of these drugs, but may contribute to the fatal ending in poisoning. The *symptoms* are those of asphyxia. There is a peculiar blue tint about the lips and finger nails. In severe cases the blood is chocolate-colored and thick, the urine discolored, the respiration increased in rate and volume, the pulse rapid.

Muscular weakness develops, followed by collapse, unconsciousness and death by respiratory failure, sometimes preceded by convulsions. The methemoglobin gradually returns to oxy- or reduced hemoglobin after death, so that an examination after several days may fail to reveal its presence.

Most of these drugs transform the hemoglobin inside the corpuscles, without injuring the vitality of the latter; but some cause, in addition, a *breaking up of the corpuscles*, and the proteins and other substances liberated produce injury to the kidney—albuminuria, glycosuria, methemoglobinuria, and the like. It is also claimed that it causes the sudden formation of fibrin ferment, which may then cause extensive intravascular clotting. The debris is credited with causing emboli. A small destruction, such as may be caused by the subcutaneous injection of glycerin, has no permanent injurious effect. The destruction of the corpuscles produces anemia, which in turn stimulates the bone marrow, so that with chronic exposure the blood count may be increased, with decreased color index, and imperfect cells in the blood stream.

The specific action of the drug is joined to these methemoglobin effects, and may entirely overshadow them. Thus, rabbits die of potassium chlorate before it comes to any methemoglobin formation. Herbivorous animals are, as a rule, much less subject to the formation of methemoglobin during life, although their shed blood does not differ in this respect from that of carniverous animals (Hanzlik and Richardson, 1934).

Hemin compounds occur as "*cytochrome*" in all cells, including plants, bacteria and yeasts (Keilin, 1925). Hans Fischer showed that yeast can synthesize hemin from porphyrine and iron. **Hematoporphyrin** is hematin with the FeOH group replaced by H_2, but retaining the four-linked pyrrole group. **Hemocyanin,** the copper-containing oxygen-conveying pigment of crustacean blood (which is blue when oxygenated, colorless when reduced) can also yield oxygen to mammalian tissue. It does not pass into the urine (R. Bing, 1938).

Intracellular Oxidations.—The food materials in the tissues are not readily oxidized by molecular oxygen, at body temperature. Oxidative metabolism is accomplished for the most part by various "chains" of oxidation-reduction of graded potentials, activated by special enzymes, which transfer hydrogen atoms from the substrate through a series of chemical "carrier" compounds until it finally unites with oxygen. The cellular oxidizing ferments are generally made up of two components, a specific protein component and one or more nonprotein substances, "co-enzymes," often related to the B-complex vitamins; thiamine, nicotinic acid, riboflavin and ascorbic acid are especially important for the intermediate metabolism of carbohydrates. The co-enzymes are not merely accelerators, but essential links in the chain, uniting with hydrogen and passing it on to the next compound. Neither enzyme nor co-enzyme of these systems can act without the other (review, C. A. Elvehjem, Wilson *et al.*, 1942; E. S. G. Barron, 1939; A. Szent Györgyi, 1938).

The oxidation systems involve chiefly three types of enzymes: (1) *Dehydrogenases*, which cause the "donation" of hydrogen to a suitable "acceptor," eventually combining with oxygen to form hydrogen peroxide or water. One group, the "aerobic," use molecular oxygen directly; the "anaerobic" require the cooperation of some other system, such as cytochrome, "yellow enzyme," methylene blue and other redox dyes of similar potential. (2) *Oxidases, which activate oxygen without the intervention of peroxide*, appear to be metallo-proteins. The most important is *cytochrome*, or indophenol oxidase, which occurs probably in all cells, plant as well as animal. It has been estimated that about two-thirds of the normal respiration of most animal tissues occurs through cytochrome. It is an iron compound, a heme derivative, a mixture of three hemochromogens, A, B and C, originally described as myohematin by MacMunn, 1886, and rediscovered by D. Keilin, 1925. It is especially abundant in the rapidly contrasting muscles of insects. Its oxidizing action is inhibited by reagents that stabilize metal groups, especially by cyanide, hydrogen sulfide, sodium azide, carbon monoxide. The CO inhibition is reversed by light of definite wave length (F. J. Ogston and Green, 1935). Formaldehyde and aliphatic narcotics inhibit its oxidation, but not its reduction. Warburg's theory (1928) attributes cellular oxidation to the catalysis by the heme iron of the "respiratory enzyme" (indophenol oxidase). (3) *Catalase*, which decomposes hydrogen peroxide into water and ordinary oxygen, and *peroxidase*, which decomposes peroxide and activates the liberated oxygen toward readily oxidizable substances, are also hematic derivatives, but they are probably not important in cellular oxidation (G. Bancroft and Elliot, 1934).

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HYDROCYANIC ACID AND CYANIDES

Hydrocyanic (prussic) acid is perhaps the most rapidly acting poison. It produces death with asphyxial symptoms, by hindering the oxidative processes of the tissues. It also interferes with most catalytic reactions and is therefore a general protoplasmic poison. Compounds containing the CN radical are toxic only if they can liberate HCN. Ferro-, ferri- and sulfocyanides (thiocyanates) are stable and therefore do not show these effects.

Occurrence.—Hydrocyanic acid exists in glycosidal form as *amygdalin* in many plants, especially in the seeds and leaves of the cherry, almond, peach, and so on. This amygdalin, when pure, is almost entirely harmless, except as it is decomposed in the body. But in most plants it coexists with the ferment emulsin, by which it is split up in the presence of water into hydrocyanic acid, glucose and benzaldehyde. One Gm. of cherry kernels yields 1.7

mg. of hydrocyanic acid; 1 Gm. of bitter almond pulp yields 2.5 mg. of hydrocyanic acid. The ancient Egyptians are said to have prepared it as a poisonous extract from peach and other plants, and the Romans used these as a suicide poison (Blythe).

The most important cyanogen (CN) compounds are the acid (prussic acid, official as the dilute, 2 per cent solution) and cyanide of potassium. Mercury cyanide has mainly a mercury action. The cyanide action is also shared by the organic esters (*nitriles*); these differ from potassium cyanide only in the rapidity with which the cyanogen is liberated (Lang, 1894; Heymans and Masoin, 1897, 1901; R. Hunt, 1904).

Etiology of Acute Cyanide Poisoning.—Hydrocyanic acid is rarely used in criminal poisoning (0.5 per cent of the recorded cases), because its quick action leads to the detection of the crime; but cyanides are often employed in suicide. Death is prompt and practically certain in spite of any treatment, if enough has been taken. Potassium cyanide can be easily obtained through its technical uses in photography, electroplating, cleaning of metals. Many fatal accidents have occurred from fumigations with the gaseous acid.

Pure hydrocyanic acid is very volatile and toxic. Scheele, who discovered hydrocyanic acid, was killed by the vapors set free in the breaking of a flask of this fluid.

Hydrocyanic acid gas fumigation is effective against all forms of vermin, "from rats to roaches" (McClintock et al., 1911). It is also used extensively for fumigating food, as well as other goods, and houses. It is safe if it is properly applied and followed by thorough airing (A. Cousineau and Legg, 1935). It is available as liquefied gas in steel cylinders, or it may be produced by the reaction of sodium cyanide with 50 per cent sulfuric acid, or with sodium chlorate and 50 per cent hydrochloric acid; or it may be solidified by adsorption on fullers' earth or on unsized paper disks. It is not injurious to most goods; it is not corrosive, and a concentration that kills rats does not injure the flavor of tea or tobacco; but fumigated eggs usually do not hatch. It penetrates readily, so that weevils in the center of a car of flour are killed by six hours' exposure. Aeration removes it completely and rapidly, so that an hour's airing renders a mattress safe for sleeping; but water holds it tenaciously, especially if cold. The objectionable feature is the *liability to accidental poisoning*. This depends partly on the facilities for diffusion: In the open air it dissipates so rapidly that it is difficult to reach fatal concentration. It effuses through brick walls, although rarely in the time of a fumigation, unless there are cracks. Careful technic is necessary to render it safe. Good protection is furnished by masks charged with a mixture of charcoal, sodium hydroxide and pumice; but toxic quantities may be absorbed by the skin on prolonged exposure. Detoxification of the air should be tested by benzidine acetate: copper acetate paper. Fire usually burns HCN to innocuous gases (C. L. Williams, 1931). It is said that about 5 to 10 per cent of people are unable to detect the characteristic odor. Lacrimator gases have been added as a warning, but are not reliable, as their diffusion is different.

The *minimum lethal concentration* for cats is about 0.35 mg. of HCN per liter of air; severe but not fatal symptoms may arise with five or ten minutes' inhalation of 0.1 mg. per liter; 0.05 is tolerated for hours (Flury and Wolfgang, 1919). The toxicity of HCN in air is reviewed critically by Barcroft, 1931. Calcium cyanide solution is a convenient means of exposing animals to constant HCN gas concentrations (Robbie and Leinfelder, 1945). The *absorption of HCN and other gases by the skin* was tested on the arm, by Schultze, 1927. It may reach dangerous proportions in twenty-seven minutes. It has been studied on animals by Flury and Walther, 1942. *Hydrogen sulfide* proved dangerous in sixty minutes, if high concentrations were used. *Carbon monoxide* and *aniline* vapor were practically not absorbed. Guinea pigs and rabbits are readily killed by absorption of HCN gas through the skin. *Spilling of cyanide solution on the skin* is not likely to be toxic, in view of the high volatility.

The fatal dosage of absorbed HCN for man is calculated as 0.7 to 3.5 mg. per Kg. (Halstrøm and Møller, 1945).

Clinical Phenomena of Acute Poisoning by Swallowing Solutions of Hydrocyanic Acid or Cyanides.—In the so-called *apoplectic form, i. e.*, when very large doses are taken, the patient may fall unconscious, often with a loud cry, within ten seconds, and die within two to five minutes, after some convulsions. Ordinarily several minutes may elapse after taking the poison before any effect is noticed; death occurs between fifteen minutes to an hour. The *symptoms* are vertigo, mental dimness, headache, palpitation; then dyspnea, which may be great; the patient then becomes totally unconscious and undergoes violent convulsions. During this stage the heart may be greatly quickened. The respiration becomes difficult and then ceases. The heart at this time is much weakened, but still continues to beat for a short time and then stops. The *mortality* is high: 95 per cent. If the patient survives an hour, *recovery* is the rule. It is often followed by persistent headache, tremors, and so forth. The prompt *diagnosis* of cyanide poisoning is important in view of the treatment. The odor is characteristic, as is also the rapid onset of the symptoms.

At the *autopsy*, the *odor* is noticeable on opening the body. There are no peculiar *lesions*, except with potassium cyanide, which acts as an alkaline caustic. The *blood* is generally liquid and remains so after removal from the body (by interference with the fibrin ferment). Its color is stated to be very dark, but this is not true of all cases: it may be of a bright arterial color. Bright red *ecchymotic* spots, due to cyan-hemoglobin, occur during putrefaction. The final *proof* of cyanide poisoning rests on chemic tests. The poison disappears within two weeks during putrefaction; but remains for a long time if the latter is prevented and if there is no evaporation. *Tests* and the quantitative determination in human tissues are described by Gettler and Baine, 1938. The *strength* of the official (dilute) acid should be 2 per cent, but many samples are much weakened by decomposition. Potassium cyanide is also variable. The pharmacopeia requires a strength of 90 per cent, but the commercial article sometimes contains only 30 to 40 per cent. This accounts in part for the variability in the severity of the symptoms. Another variable factor is the *rate of absorption*. If the stomach is full there is much better chance of saving the patient. Application to raw surfaces or to cuts has given rise to poisoning. The *fatal dose* of absolute HCN is about 0.05 Gm. (1 grain); that of KCN is 0.2 to 0.3 Gm. (3 to 5 grains); that of dilute hydrocyanic acid would be about 2.5 Gm.; 50 to 60 bitter almond seeds would be fatal. Correspondingly larger doses are needed if the drugs are impure or decomposed. The impression prevails widely that prussic acid is one of the most powerful poisons. This reputation is based on its *extremely rapid action*, rather than on its toxic dose.

Chronic Poisoning.—Repeated administration of sublethal doses of cyanides was said to lead to chronic cachexia, without altering the susceptibility to the poison (Schlegel, 1892). Peripheral neuritis has been reported (Collins and Martland, 1908). However, C. J. Reed, 1920, found neither chronic symptoms nor increased susceptibility in dogs exposed daily to sublethal doses of cyanide vapor. Chronic poisoning may be produced by *foods* containing cyanic substances, such as cassavas in Africa, and fermented maize. A. Clark, 1939, found visceral and nervous degenerations in such cases. The glutathione level of the blood had fallen to half the normal level.

Symptoms of Poisoning by Cyanide Gas.—Concentrations of 2 or 3 oz. per 1000 cubic feet produce no noticeable effects within half an hour. Concentrations used to kill rats, 6 to 10 oz. per 1000 cubic feet, cause immediate and progressive *sensation of warmth* over the entire body, due to vasodilatation, with visible rubefaction in five minutes. This is a danger signal. If the exposure is continued, it is followed by prostration, then nausea and vomiting, often with headache; then by difficult respiration, with sensation of tight bands around the chest. This is the final warning. It is soon followed by loss of consciousness, then within ten minutes by paralysis of the respiration and prompt death. Exposure to convulsive concentrations for fifteen minutes is almost always fatal, even if the animal is then removed from the poisoned atmosphere; if convulsions have started, treatment is ineffective. If the unconscious patient is brought into the open air before breathing stops, he usually *recovers* unaided. Nausea, vomiting, fast pulse and headache may last for a time, but he is able to walk home, and is practically well in two or three days, without any serious sequels. If the respiration is stopped, but the heart is still beating, artificial respiration generally leads to recovery, but the after-effects are more severe. A "weak heart" may persist for months. If the heart has stopped beating, there is no hope of recovery.

If lower concentrations of cyanide gas are breathed over longer periods, one-half to several hours, the course is somewhat different, and may take two directions: (1) The patient may lose consciousness, but continue breathing, and finally die in convulsions; or he may recover after several hours of coma, usually followed by extreme weakness and headache, and a slow convalescence of half a year to a year, before the normal is restored. Asphyxial cerebral degenerations may be assumed. (2) Other patients retain consciousness, but fall dead of heart failure on making some extra exertion. Subconvulsive concentrations of cyanide can be prolonged indefinitely, as the natural detoxifying mechanisms are practically inexhaustible, although slow (C. L. Williams, 1931, clinical; E. Heldorf, 1939, dogs). *Cyanide dermatitis* has been described (ref., J.A.M.A., *95:*1690).

Effects on higher animals consist in *fleeting stimulation of certain parts of the central nervous system, followed by depression and paralysis.* The action *begins in the medulla.* The vomiting, respiratory, vagus, pupil-dilator and vasomotor centers are all stimulated, in part reflexly from the carotid sinus. Then comes *unconsciousness,* and after this *convulsions.* In man these are probably mainly medullary in origin. They are followed by paralysis of the whole central nervous system. Involuntary evacuations of feces, urine and semen are frequent.

The **respiration** is at first greatly increased, especially in depth; it then becomes slow, shallow and irregular (Cheyne-Stokes type). It stops considerably before the heart, paralysis of the respiratory center being the immediate *cause of death.*

Respiration is more sensitive to cyanides than the vasomotor center, and this again is more sensitive than the vagus center. Larger doses slow the rate, but greatly increase the depths of respiration. Toxic doses depress and paralyze the center. Boehm and Knie, 1874, showed that the hyperpnea is not due to a reflex arising in the lungs, for it is not affected by section of the vagi (nor by atropine). It was attributed to direct stimulation of the respiratory center, until Heymans showed that the hyperpnea and bradycardia result almost altogether from stimulation of the chemoreceptors of the carotid glomus and aortic body (Heymans, Bouckaert *et al.*, 1932; Winder *et al.*, 1933; Comroe and Schmidt, 1937). *Direct action on the respiratory center* is subordinate; but painting the floor of the fourth ventricle with sodium cyanide produces stimulation (Owen and Gesell, 1931). In *frogs,* the respiratory center is also stimulated by small and depressed by large doses.

Pyruvic acid cyanohydrin, injected into dogs and cats causes prolonged stimulation of respiration and counteracts respiratory depression by barbiturates and morphine. It is effective when CO_2, metrazol and lobeline fail. It also acts mainly through the sinoaortic reflex (E. K. Marshall and Rosenfeld, 1937).

Clinical Use for Respiratory Stimulation.—The intravenous injection of sodium cyanide is the most potent available measure for stimulating the respiratory center. The effective dosage (0.05 mg. per Kg. for animals) is about 1/20 of the minimal fatal dose, so that there is an ample margin of safety; and the cyanide is so rapidly detoxicated by conversion into thiocyanate that cumulation can be easily avoided. The effects of a single injection are not lasting (rarely longer than ten seconds), but they can be repeated as desired, or they may be maintained by continuous injection. The usefulness is limited by the fact that the presence of cyanide prevents the tissues from utilizing the oxygen; but this becomes available when the cyanide is destroyed. It therefore seems advisable to make the injections intermittently. In drowning and in anaesthetic poisoning, the increased respiratory movements help to clear the air passages of obstruction or poison.

For this purpose, the starting dose should be 5 cc. of a 0.1 per cent solution, for man. The ordinary dosage is 1 cc. for this solution. This may be repeated indefinitely, at a rate not faster than every fifteen to thirty seconds. It should be discontinued on the appearance of marked pallor, nausea, marked increase of pulse rate, or depression of respiration. The solution must be freshly made by dissolving 100 mg. of sodium cyanide in 100 cc. of normal saline, without the use of heat. Hypodermic or intramuscular injection is not feasible, as the dose and effect cannot be adjusted with sufficient accuracy (Loevenhart *et al.*, 1918).

Convulsions.—Rabbits deprived of their hemispheres exhibit the usual type of convulsions, but the course is more rapid (Morita, 1915). In frogs, doses of cyanide which are ineffective alone evoke convulsions with subconvulsive doses of brucine, hydrastine and coramine (Bergstermann and Krauskopf, 1938).

The effects on the circulation are those of anoxia. As in the latter, the heart may again execute a few movements after it has stopped for a time, but these do not suffice to maintain the circulation. The *bradycardia* is due practically entirely to carotid and aortic reflex. However, the response to electric stimulation of the peripheral stump of the divided vagus is also increased (Danilewsky and Wjalkowa, 1931). The *vasomotor center* shows intense stimulation, with corresponding rise of blood pressure, as in asphyxia (Pilcher and Sollmann, 1915). The rise is chiefly reflex from the carotid sinus and aortic arch, but the vasomotor center plays a larger part than with the respiratory stimulation (Heymans *et al.*, 1932). The share of the aortic body is larger than that of the carotid body (Comroe, 1938). In *excised kidneys* perfused with saline solution, the addition of hydrocyanic acid causes marked dilatation of the renal vessels. The effect is apparently due to a paralysis of the arterial muscle. It disappears promptly on removing the cyanide (Sollmann, 1908). In heart-lung-kidney preparations it abolishes selective reabsorption by the tubular epithelium. In intact animals small doses of cyanide produce spasm of the glomerular vessels and decreased output of urine (Richards *et al.*, 1938). The *coronary vessels* are also dilated (Loevenhart and Eyster, 1931; G. T. Kent *et al.*, 1939). Applied directly to the *frog's heart*, cyanides cause standstill which is not removed by atropine; the heart responds strongly, however, to electric or mechanical stimulation. There is no evidence of this action on blood pressure tracings from mammals. *In limulus*, weak concentrations stimulate the heart muscle and ganglia (Carlson, 1907).

Excised Intestines.—Potassium cyanide interferes with the contractions, especially of the higher portions, in which metabolism is probably more active (Alvarez, 1918).

Local Anesthesia.—Direct application of HCN to the intact skin produces local anesthesia. It has been used as an anodyne in pruritus, and against cough and vomiting; but it is not very effective and the danger of fatal mistakes renders its use inadvisable.

Metabolism.—Severe cyanide poisoning increases the total N excretion, mainly as urea, both in starving and in fed animals. Injection of cyanide into anesthetized rabbits results in immediate increase of *oxygen consumption*, followed by a severe drop (K. O. Möller, 1935). The *glutathione* and *lactic acid* of rabbit *muscle* are reported increased after subconvulsive and convulsive doses of cyanide (Handovsky, 1928). The lactic acid content of the *brain* rises materially (W. E. Stone, 1938).

Growth and Tumor Development.—Long-continued inhalations of HCN gas arrest body growth in young rats and retard the growth of Jensen rat sarcoma transplants, often with regression of the tumor and lessened takes of retransplants. The effective dose is close to the lethal (L. Karczog, 1927; I. H. Perry, 1935).

Phagocytosis is stimulated *in vitro* by traces of KCN, the effect being analogous to oxygen deprivation (H. J. Hamburger, 1915). Intravenous injections of cyanide intensify *mustard conjunctivitis* (Amberg *et al.*, 1917).

Lower Organisms.—Cyanide is a *violent protoplasmic poison*, presumably through its interference with enzymes which play a most important role in life processes. All forms of life, all tissues and organs, are affected. Infusoria are killed in a concentration of 0.1 per cent. The growth of yeast and of higher plants, the germination of seeds, the contractility of animal cells, the conductivity of nerves, and so forth, are inhibited. If the action is sufficiently continued, all vitality is destroyed; but if the cyanide is promptly removed, complete recovery occurs. Its effects agree with those of deprivation of oxygen. Amphibian eggs can develop in cyanide up to the beginning of gastrulation, and are then arrested. *Sodium azide* arrests development in all stages, from fertilization on (Spiegelmann and Moog, 1945). In certain fish ova, cyanides suspend the autolytic processes accompanying death, so that the cells remain in a condition between life and death for several days (Sollmann, 1906). Sodium cyanide inhibits putrefactive *bacteria* in the diultion of 1:25,000, but it is not a potent bactericide. Green *plants* are killed when the air contains 0.02 to 0.2 per cent of HCN; the germination of *seeds* is stimulated by these concentrations (C. Wehmer, 1918). The *site of the toxic action on cells* appears to be the cell membrane, for concentrations which kill amebae promptly on immersion, fail to kill them if injected into the cell, in one-half of the volume of the cell (Brinley, 1928). Presumably the cyanide forms reversible compounds with oxidases on the cell surface, that are necessary for oxygen uptake into the cell (A. J. Clark, 1937). Even very dilute cyanide solutions increase the *permeability* of Tradescantia cells. This effect is enhanced by low concentrations of chloroform or alcohol; diminished by higher concentrations (Krehan, 1914).

The cyanide inhibition of yeast growth is antagonized by yeast extract, but not by any isolated constituent (M. A. Eppright and Williams, 1947).

Cyanide Action as Tissue Asphyxia.—The phenomena of the action of hydrocyanic acid on the central nervous system—the stimulation of the medullary centers, the convulsions, the vascular paralysis, and the like—bear a close resemblance to those of asphyxia and it can be shown that oxidation is enormously diminished. There is, however, one marked difference from ordinary asphyxia, for the blood remains of a bright arterial color; indeed, the oxygen content of the venous blood in typical cyanide poisoning approaches that of ordinary arterial blood (Cl. Bernard); the red color of the venous blood is partly due to more rapid circulation from vasodilatation and cardiac stimulation (Chio, 1911). The oxygen is in the ordinary combination with hemoglobin, and can be removed as readily as normally *in vitro;* for instance, by a vacuum (C. L. Evans, 1919). It is therefore evident that the oxygen supply to the tissues is not lessened. The cause of the asphyxia, of the lessened oxidation, must lie in the protoplasm of the tissues. This undergoes "*internal asphyxia,*" in sight of abundant oxygen (Geppert, 1889). Cyanide asphyxia is more promptly fatal than is complete exclusion of oxygen, for in the latter event the cells can use the oxygen as long as any is left in the blood. The interference with oxidation has also been demonstrated with "salted frogs"; excised kidneys (Vernon, 1906); many lower animals; and with ferments. *In vitro,* cyanide inhibits all but 2.5 per cent of the oxidation of brain tissue, indicating that brain respiration is effected through the *cytochrome* system (review, J. H. Quastel, 1939).

Action on Hemoglobin.—It is doubtful whether HCN combines directly with hemoglobin under the conditions of the body (v. Zeynek, 1901). When added to methemoglobin, however, it causes the formation of *cyanhemoglobin* (Kobert, 1891) with a characteristic spectrum band. This is responsible for the bright red ecchymotic spots seen after hydrocyanic poisoning. Methemoglobin can be used as a test for hydrocyanic acid. The cyanhemoglobin formed by treating washed erythrocytes of dogs with nitrite and then with cyanide, is not toxic on intravenous injection, even in quantities equivalent to six fatal doses of free cyanide. It is gradually reconverted into functional hemoglobin at the same rate as methemoglobin, suggesting that the cyan is gradually liberated and detoxified (Etteldorg and Morrison, 1940). M. M. Brooks, 1935, denies the existence of cyanhemoglobin.

Oxidation in Invertebrates.—Oxygen consumption in *sponges* is first increased, then diminished. High concentrations produce practically pure depression (Hyman, 1916). In *planaria,* G. Allen, 1919, found the oxidation reduced by 30 per cent through minute doses of cyanide. Larger doses caused a further reduction to 20 per cent, beyond which there was no other reduction, even with larger doses. The action is reversible, *i. e.,* rapid and complete recovery occurs after removal of the cyanide. The respiration of *paramecium* is partially inhibited by cyanide, the extent depending on the supply of carbohydrate food. Starved and aged organisms are relatively insusceptible (D. M. Pace, 1945).

Action on Enzymes.—Schoenbein, 1867, first showed that hydrocyanic acid inhibits oxidizing ferments, preventing the catalytic action of shed blood on H_2O_2. The *catalase* is not destroyed, but only inhibited. (In acute cyanide poisoning, the inhibitory concentration is not reached; Duncker and Jodlbauer, 1911.) The *cytochrome* (indophenol) oxidase system is highly sensitive to cyanide (also to *azide*); if oxidation is not inhibited by these, it is not effected by cytochrome. The converse does not hold. It increases the adenosine triphosphate activity of myosin and nullifies the inhibiting effect of copper (F. Binkley *et al.,* 1944). It has a similar inhibitory effect on many other organic ferments and inorganic catalyzers (spongy platinum). The effect on metals is probably produced by a minute film of cyanide, and its mechanism is therefore probably not analogous to that on organic ferments.

The maintenance of the high energy phosphorus compound appears to be mediated largely through the cytochrome oxidase system which is inactivated by cyanide (H. G. Albaum *et al.,* 1946).

Fate.—Hydrocyanic acid changes readily by exposure to light and air and undergoes rapid decomposition in the body. Part of it combines with sulfur-containing molecules to form thiocyanate, part is excreted unchanged by the lungs. The fate of the remainder is unknown. Post mortem, Waller, 1910, found the largest quantity in the heart and brain; but it disappears in a few days by transformation into thiocyanate (Chelle, 1919; Kohn, Abrest and Lupis, 1928). Cyanide disappears when incubated with *serum,* the loss being proportional to the dextrose content.

The *limited detoxicating efficiency of thiocyanate formation* is illustrated by the fact that the toxicity of 0.001 per cent of NaCN solution, perfused through the toad heart, is not antagonized by the addition of $NaHSO_3$; nor does perfusion with the latter hasten recovery (Combes, 1927). *Thiocyanate formation from nitriles* can be demonstrated on pigeons, whose blood does not normally contain SCN, but does so if cyanide, propionitrile or phenylacetonitrile are administered (Tsurw, 1933).

Treatment of cyanide poisoning is of limited efficiency, because of the rapid course and by the inherent gravity of any degree of tissue asphyxia. Attempts have been made to evacuate and to destroy the cyanide in the stomach, especially by oxidation, and after absorption to convert it into firm compounds, especially by methemoglobin, thiosulfate, colloidal sulfur or certain sugars.

Routine Clinical Management of Cyanide Poisoning (based chiefly on Hanzlik and Richardson, 1934).—One of the oral antidotes should be given as promptly as possible—animal charcoal, hydrogen peroxide (1:5), permanganate (1:1000) or sodium thiosulfate, 5 per cent; followed as promptly as possible by gastric lavage with one of these solutions, diluted 1:10. Brisk respiration should be maintained, mechanically or by 5 per cent CO_2 in oxygen. As promptly as possible 1 per cent sodium nitrite should be injected into a vein, slowly, in 10 cc. doses, to a total of 50 cc. in an hour. Epinephrine should be in readiness against excessive fall of blood pressure. Between nitrite injections, 20 cc. of 5 per cent sodium thiosulfate should be injected intravenously and if necessary continued to a total of 500 cc. In place of the nitrite, methylene blue may be injected intravenously, 50 cc. of 1 per cent in isotonic (1.8 per cent) sodium sulfate, repeated as needed to a total of 200 cc. If the patient becomes too much cyanosed from the methemoglobin, blood transfusion may be used. The fatal dose of hydrocyanic acid for man is about 0.05 Gm.; for potassium cyanide, about 0.25 Gm.; but the latter varies with the acidity of the stomach. The tabulated efficiency of treatment in dogs (see below) indicates the maximal doses that might be survived under treatment.

Hydrogen peroxide forms oxamide: $2HCN + H_2O_2 = (CO)_2(NH_2)_2$. *Cyan-metal compounds* are formed too slowly to be of much practical value. *Alkaline ferrous sulfate* forms the nontoxic ferrocyanide, but is too slow to be reliable. It was advocated by Smith, 1884, and again endorsed by Sandwick, 1906. It is prepared by mixing ferrous sulfate solution with milk of magnesia, or with sodium bicarbonate solution. Similarly, cobaltous nitrate (administered as 0.5 per cent solution) forms cobaltocyanide. It has not come into clinical use.

Brisk respiration favors the excretion of the cyanide by the lungs—it is not generally needed to supply oxygen. It is useless in collapse, when the circulation is slow. It should therefore be begun early, and continued until the circulation fails. Counterirritation and general stimulants such as caffeine, atropine and metrazol are probably of no value.

Thiosulfate ("Hypo"), $Na_2S_2O_3$; tetrathiosulfate, $Na_2S_4O_4$; and other sulfur compounds and colloidal sulfur simulate the natural detoxication of cyanide, by forming thiocyanate, SCN, which lacks the cyanide action and is practically nontoxic. The slowness of the reaction greatly limits its usefulness in acute poisoning. Thiosulfate is of little use in the stomach, and is but slowly absorbed. It is best administered intravenously (A. Buzzo, 1932).

In animal experiments, using generally rather larger doses than would be safe clinically, it is successful as a prophylactic, especially in the slowly developing nitrile poisoning (Heymans and Masoin, 1897), but is not brilliant in the developed poisoning. It is most useful in combination with the methemoglobin-forming antidotes, which secure more time for the thiocyanate formation. This occurs but slowly with thiosulfate, in life and in the test tube.

Thiocyanate Formation.—Intravenous injection of NaCN, 1 mg. per Kg., into dogs doubles the thiocyanate content of the serum within half an hour, and this continues to rise to a maximum of two to eight times the normal, in two to five hours (R. G. Smith and Mukerji, 1939).

Sulfur on Thiocyanate Formation.—Colloidal sulfur forms thiocyanate slowly in acid solution, but practically at once in alkaline solution (E. Milanesi, 1926). This led to the suggestion to administer colloidal sulfur as such, suspended in sodium bicarbonate solution (A. W. Forts, 1928). In life tests, however, the antidotal superiority of colloidal sulfur over thiosulfate is not striking.

Tetrathiosulfate was introduced by A. Chistoni and Foresti, 1932, with the claim that it is speedily effective and superior to thiosulfate and colloidal sulfur, but others found no material difference from thiosulfate.

Methemoglobin Formation.—Methemoglobin binds cyanide promptly and firmly to form cyanhemoglobin, which is nontoxic, perhaps because it does not penetrate into the cells. All methemoglobin formers therefore antidote cyanide; but cyanhemoglobin and methemoglobin are not oxygen carriers. Since at least a third of the hemoglobin must be kept in function, this sets a quantitative limit to the antagonism, which lies practically at 3 to 4 fatal doses. It may be extended somewhat by transfusion; in any event, it acts immediately and provides an opportunity to supplement it by the more slowly acting thiosulfate. Any agent would be suitable which forms methemoglobin promptly *in vivo*, without destroying the corpuscles or being otherwise toxic. Practically, the two most available agents are sodium nitrite and methylene blue.

Sodium nitrite (introduced by E. Hug, 1932) is the more effective, but the optimal dosage for animals (10 to 20 mg. per Kg.) might be dangerous clinically (fall of blood pressure). However, the doses advised above appear safe. Amyl nitrite may be used, but it has no advantage and the patient is probably more liable to collapse.

Methylene blue has been used perhaps more extensively in the clinic, although in animal experiments it is somewhat less effective than nitrite; it does not potentiate as well with thiosulfate and probably has more toxic side actions.

Quantitative Comparison of Cyanide Antidotes.—Rabbits are not suitable for methemoglobin-forming antidotes, nitrites and methylene blue (W. Heubner, 1927). With dogs, which are probably fairly comparable with man in this respect, Chen, Rose and Clowes, 1934, found the treatments to protect against the following number of hypodermic fatal doses of sodium cyanide (6 mg. per Kg.) (in ascending order): methylene blue = 2; sodium thiosulfate and tetrathiosulfate = 3; sodium nitrite and amyl nitrite = 4; methylene blue plus tetrathiosulfate = 6; amyl nitrite plus thiosulfate = 10; sodium nitrite plus thiosulfate = 20.

The *efficiency of methylene blue* in cyanide poisoning was first shown by Sahlin, 1926, and established by Eddy, 1930 and 1931. Its first clinical use was by Geiger, 1932, at the suggestion of Hanzlik. The question is still open as to what extent the methylene blue acts through methemoglobin formation, and to what extent through other actions. The peculiar oxidation-reduction action of methylene blue suggested a direct antagonism, the methylene blue acting as a substitute for the normal cellular oxidation catalysts inactivated by the cyanide; this explanation was developed especially by Sahlin, by Eddy and by M. M. Brooks, 1932, 1939; but Hug, 1932, suggested that it acts chiefly by forming methemoglobin; this was supported by Wendel, 1933, and is probably most generally accepted as the main factor, chiefly because with rabbits, which do not readily form methemoglobin, methylene blue is not an effective cyanide antidote. Ethylene blue, which does not form methemoglobin, is also ineffective as a cyanide antidote (Hanzlik and Richardson, 1934). Haggard and Greenberg, 1933, found that methylene blue converts 8 to 12 per cent of the hemoglobin of blood into methemoglobin, in the test tube. The excess of dextrose interferes, however, with the formation of methemoglobin by methylene blue (but not by nitrite; Warburg, Kubowitz and Christian, 1930), and Brooks, 1934, denies that methylene blue forms methemoglobin in living dogs. Methylene blue has marked pharmacologic actions (hyperpyrexia, and so forth), and when Sahlin discovered the antidotal value of methylene blue he considered it as probably too toxic to encourage its practical employment. This limits the dosage, but it appears safe in the quantities which have been employed clinically. Its clinical efficiency, however, is dubious, notwithstanding the earlier glowing reports, as it is not certain that the outcome would have been fatal even without treatment. Trautman, 1933, found it of no value under practical conditions and against inhalation of cyanide vapors in lethal or near lethal doses, for rabbits, rats and guinea pigs; but these are probably not suitable est animals.

Other methemoglobin formers, pyrogallol, pyrocatechiol, phenylhydrazine and dinitrophenol, are too toxic for practical use. Potassium ferricyanide would be ineffective with intact blood, since it does not penetrate the corpuscles sufficiently readily; but if added to laked blood and injected, it is fairly effective (Hug, 1932). However, the renal excretion of methemoglobin when dissolved in the plasma reduced its efficiency.

Sugars, Aldehydes and Ketones as Cyanide Antidotes.—Of various sugars that have been tried, triose (glycerinic aldehyde) has been the most successful (A. W. Forst, 1932), but not so good as nitrites. It acts by the formation of the nontoxic cyanhydrin (H. Casser, 1930), possibly assisted by central actions. Zanda and Atzori, 1938, found that detoxication of cyanide by glucose *in vitro* requires two hours, which would be too slow for a clinical antidote. The chemical reaction involves an equilibrium constant, which was determined for various aldehydes and ketones by E. K. Marshall and Rosenfeld, 1934. Dihydroxyacetone (oxantin) acts briefly and thus secures time for thiosulfate (Forst, 1928; B. B. Turner and Hulpieu, 1933), but by itself is less effective than triose. Forst claimed some benefit from glucose, about the same with and without insulin, but Turner and Hulpieu found it ineffective. They point out that cyanide itself tends to raise the blood sugar markedly, proportional to the severity of the symptoms.

Acrylonitrile (vinyl cyanide) is used in the manufacture of synthetic rubber. Exposure to the vapor produces typical nitrile effects, *i.e.* somewhat slowed cyanide poisoning, with respiratory stimulation and convulsions; death may not occur till many hours after the exposure. Thiocyanate is increased in the blood and urine. Sodium nitrite antagonizes the effects. Susceptibility varies considerably in different species. The minimal fatal concentration for dogs, which are relatively susceptible, is 0.25 mg. per liter of air, equivalent to 110 ppm. Daily exposure to sublethal concentrations produces irritation of the eyes and nose, gastro-intestinal disturbances and weakness of the hind legs, with relatively rapid recovery. Autopsy shows renal irritation in most of the animals, subacute bronchopneumonia in most except cats, liver damage only in cats (H. C. Dudley *et al.*, 1942).

Complex CN Compounds.—*Sodium ferricyanide*, $Na_3Fe(CN)_6$, and *ferrocyanide*, $Na_4Fe(CN)_6$, are not toxic as such, since the CN is bound. Dogs tolerate intravenously 35 cc. of a 7.5 per cent solution of the crystalline ferrocyanide, per Kg. of body weight, and excrete it rapidly by the urine. Poisoning is said to have occurred with oral administration from the liberation of HCN by the gastric acidity, but this has been questioned. The oral dose has been stated as 0.2 to 1 Gm. Ferrocyanide is not excreted by the aglomerular kidneys of Lophine fish (E. K. Marshall, 1930). It has been introduced as a clinical test of *glomerular function*, by intravenous injection of 0.5 Gm. of the hydrated sodium ferrocyanide (0.25 Gm. of the anhydrous) in 10 cc. of freshly distilled water. The results are fairly parallel to those of the urea clearance, phenolsulfonphthalein and urine concentration tests (E. J. Stieglitz, 1939).

Nitroprusside (sodium nitroferricyanide) is decomposed completely in the blood and tissues at body temperatures, liberating cyanide (H. E. Hill, 1942), and its toxicity is practically the same. The symptoms develop more slowly (L. W. Mahaffey, 1942). See also under *Nitrites.*

Calcium cyanamide, $CaCN_2$, is used extensively as a synthetic agricultural fertilizer. It does not contain free cyanide, but acts as cyanamide, dilating the blood vessels. The action is not cholinergic, for it is not antagonized by atropine. Slight cases of poisoning have transitory redness of the face and headache. In severe cases, the skin and mucosae show marked congestive hyperemia (especially head, thorax and lungs, if the poison is inhaled as dust), respiration is accelerated and deeper, the heart beat is irregular, blood pressure is lowered and vertigo occurs. The attack usually lasts one-half to two hours, generally with complete recovery. Large doses produce profound shock (R. D. Barnard, 1943). The fatal dose is about 40 to 50 Gm.

Cyanogen chloride, CNCl, produces cachexia on long-continued exposure (C. I. Reed, 1920). Its acute effects closely resemble those of HCN. If the vapor is inhaled it also acts locally on the respiratory passages, producing bronchial constriction and irritation. Blood corpuscles rapidly convert about 30 per cent of the CNCl into HCN; serum quickly destroys it without producing HCN (W. N. Aldridge and Evans, 1946).

PREPARATIONS.—*Diluted Hydrocyanic Acid*, N.F., contains about 2 per cent of HCN. On standing, it loses strength rapidly, decomposing into ammonium formate, CO_2, cyanic acid, and a brown precipitate of paracyanogen (L. A. Brown, 1910). The decomposition is retarded by acid, alcohol and acetanilid (Coblentz and May, 1908). *Potassium Cyanide*, KCN, occurs usually as white, opaque masses, with cyanide odor. Dose, 5 mg., $\frac{1}{12}$ grain. Commercial samples are often impure. *Sodium Cyanide*, NaCN, white, opaque pieces, or granular powder; deliquescent in the air and exhaling the odor of hydrocyanic acid. Freely soluble in cold water. *Oil of Bitter Almond*, U.S.P. (Ol. Amygdalae Amare), a volatile oil distilled from Amygdalus communis or other sources. Yields not less than 95 per cent of benzaldehyde, and not less than 2 per cent or more than 4 per cent of hydrocyanic acid. *Not to be used or sold for flavoring foods.* Dose, 0.03 cc., $\frac{1}{2}$ minim. *Wild Cherry Bark*, U.S.P. (Prunus Virginiana), the stem-bark of Prunus serotina; contains tannin, amygdalin and bitter glucoside. The *Syrup* represents 15 per cent of the bark. Dose, to 10 cc., $2\frac{1}{2}$ drachms; mainly as flavor for cough-mixtures.

PHYSICAL FACTORS OF "SALT ACTIONS"

Besides the properties ordinarily designated as chemical, substances in solution or suspension also have certain *physical* properties, depending on their molecular state, and independent of their chemic composition. Both the drugs and the cells have these properties.

Molecules in solution have qualitatively and quantitatively identical effects on the boiling and freezing point, on vapor pressure and on osmotic tension. Through osmosis they may alter the water and salt content of the cell, its internal pressure, the surface tension, and the electric surface potential, and consequently the functions. This may occur even though the substance itself does not enter into the cells. These effects are produced by all substances in solution, but since the results are proportional to the number of molecules dissolved in the unit volume of the solvent, their importance varies with the quantity of the drug that can be introduced without producing serious chemic changes. They are practically important mainly for the neutral salts of alkalis, and are therefore commonly called "*salt actions*." In *colloid solutions*, the solute occurs in smaller or larger groups or "aggregates" of molecules, which approach more or less in their properties to mere suspensions of solids or liquids, and exert less of the physical qualities of true solutions. On the other hand, the suspensions exhibit the electric and surface phenomena of particles. Because of the relatively high state of subdivision, the "*surface phenomena*"—surface tension, adsorption, catalytic properties, and so forth—are conspicuous and play an important part in the functionation of protoplasm. The consistency of the protoplasm, fluid or gelatinous, and the quantity of water imbibed, also depend on the colloids. These properties are influenced by the physical, electrical and chemical conditions of the medium in which the colloid is suspended.

COLLOIDAL SOLUTIONS

Relation of Colloids and Crystalloids.—Graham, 1861, divided soluble substances into crystalloids and colloids, according to whether they diffuse through parchment and similar membranes. This criterion has been supplemented by others, but the division is important and has been retained. Any substance assumes the colloidal state when it is suspended in sufficiently fine comminution, in a liquid that does not dissolve it materially in the molecular state. A "solution" may therefore be colloidal in one solvent (tannin in water), molecular in another (tannin in alcohol). As the size of the aggregates of molecules which constitute the colloid state varies, the transition between the physical properties of the two kinds of solutions is not abrupt, but gradual.

Properties of Colloids.—Each aggregate behaves like a single molecule, so that the molecular concentrations of colloid solutions are relatively low. Colloids therefore have relatively little influence on the *osmotic pressure*. One of the most distinctive properties of colloid solutions is their *turbidity*, which may be perceived directly, or only by the Tyndall phenomenon (*viz.*, a beam of light becomes visible when passed through a colloid solution). Colloids *do not dialyze* through parchment or similar membranes. *Diffusion* through the solvent is slow or practically absent. The *electric properties* are characteristic: colloids are usually electrically charged, the quantity and sign of the charge being variable at will. The important *surface actions* will be discussed later. The colloids easily undergo further aggregation to larger particles, *i.e.*, *coagulation*. Colloid solutions are often permanently changed by temporary physical conditions, such as boiling, freezing or keeping (*hysteresis*).

Suspension and Emulsion Colloids.—Colloid solutions fall into two classes: the suspension colloids, in which the particles behave as solids; and the emulsion colloids, in which they generally behave as fluid. The difference is probably one of affinity for the solvent. The emulsion colloids are *hydrophilic*, or lyophilic; they seem to attract the solvent into the aggregates which are thereby more or less liquefied. The suspension aggregates are *hydrophobic;* they do not take up water, but remain discrete and solid. The emulsoids approach more nearly to true solutions, and may sometimes consist of discrete but large molecules. They are typified by soluble proteins and are therefore of a special biologic importance. The colloid metals and sulfides, congo red, and so on, are suspensoids. The *emulsoids* form viscid solutions or jellies, lower the surface tension, and are coagulated only by large quantities of electrolytes. The *suspensoids* are not viscid, have little effect on surface tension, and are easily precipitated by traces of electrolytes.

Permanance of Suspensions.—Small particles suspended in a liquid tend to coalesce by surface attraction, to form larger particles. The molecular particles in colloid solutions have the same tendency; but since all the particles in a solution are charged with the same sign (negative electricity in most protoplasm), they repel each other. Any increase of the charge (negative in the example) increases this repulsion, and consequently diminishes the size of the aggregates. If electricity of the opposite sign (positive) is introduced, some of the charges are neutralized and the particles tend to coalesce. If this (positive) electricity is increased beyond the point when all the original (negative) charges are neutralized, the particles become charged with positive electricity, and again fly apart. These modifications may be produced by the passage of an electric current, or by the electric charges of the ions of electrolytes. Suspensions of hydrophobic colloids (such as colloidal gold) contain an infinite gradation of sizes of aggregates in the same solution; while the size of a hydrophilic colloid (such as a protein) is uniform in a given solution (Svedberg, 1938).

Precipitation of Suspension Colloids by Electrolytes.—Since suspensoids have no affinity for the solvent, they are readily precipitated when their electric charges are removed. This occurs most easily when their electric charge is already small, *i. e.*, when they approach the "isoelectric point." Minute traces of electrolytes are then sufficient. The precipitation of positively charged colloids depends mainly on the anions, that of the negative on the cations (Hardy's Law). The precipitant power of the ions is a function of their valence (Schulze, 1882, 1884), since this determines their electric activity. However, ions of the same valence are not equally active.

Fate of Intravenously Injected Colloids.—Finely divided powders or true colloids appear to be taken from the blood stream primarily by the Kupffer and other reticulo-endothelial cells. For instance, an hour after intravenous injection of finely divided MnO_2, Drinker and Shaw, 1921, found 38 per cent in the liver, 47 per cent in the lungs, 4.3 per cent in the spleen, leaving only 11 per cent for the remainder of the body; but after twenty-four hours most of the material was in the liver. Gye and Purdy, 1922 and 1924, reported that repeated intravenous injection of silicic acid produces enlargement of the fixed histologic cells of the liver, spleen and bone marrow, and their detachment into the circulation. Injections of colloidal suspensions are used experimentally to "fill up" the reticular endothelium and thus to render it functionally inactive.

Red blood corpuscles constitute a coarser suspension, but are governed by similar laws. They bear negative charges and therefore tend to be agglutinated, sedimented and precipitated by positively charged ions (acids). The rapidity with which *sedimentation of red corpuscles* occurs in shed blood varies with conditions. It is accelerated, for instance, when albumoses are injected; in the "hemoclastic crises" of colloidal and immunity reactions (Widal); in the cachexia and anemia of malignant disease (Gragert, 1923); in pregnancy (Fahraeus, 1918); and in various pathologic conditions, especially those associated with fever and inflammation (Fiedler, 1923).

Emulsions are fine and permanent suspensions of one liquid in another immiscible liquid; *f. i.*, oil in water, or vice versa. Surface tension tends to separate immiscible liquids. This tendency may be counteracted by lowering the surface tension of the dispersing medium (as by saponin or soap) or by increasing its viscosity, and by adsorbing the water by hydrophilic colloids (as by gums and proteins). The essential feature of permanent emulsion is the adsorption of a colloid on the surface of the oil droplets, coating these with a resistant membrane. Saponin, which has relatively little effect on surface tension, acts mainly in this manner (Howard and Sollmann, 1924).

The water-soluble alkali soaps secure the suspension of lipoids in water, while the oil-soluble calcium soaps change the phases so as to suspend the water in the oil. The addition of sodium or calcium ions therefore changes the phase of an emulsion, and thereby influences the permeability; the sodium soap system is freely permeable to water, the calcium system being impermeable (Clowes, 1914 to 1916).

Precipitation of Hydrophilic Colloids by Electrolytes.—These, like the suspensoids, are precipitated only by electrolytes, not by nonelectrolyzed crystalloids (the precipitation of proteins by alcohol is attributed simply to insolubility). The process, however, is probably quite different. With the emulsoids, much higher concentrations of the salts are required; the precipitation is generally reversible; electrolytes may also have solvent actions, the end result being the algebraic sum of the actions of the cation and anion (Pauli, 1905, 1908).

The ions form a regular series (*"lyotropic series"*), which is reproduced in many different phenomena. The anion series run SCN, I$<$ClO$_3$$<NO_3$, Br$<Cl<CH_3$.COO$<$-SO$_4$, PO$_4$$<$tartrate$<$citrate. With (negative) proteins, lecithin, and so forth, the left side of this series is solvent, the right side precipitant. They have a similar influence on heat-coagulation temperature; on the solubility of globulins; the solubility of gases, alcohols, and the like; on the viscidity and surface tension of water; on the saponification of esters, and so on. It has been suggested that all these phenomena can be explained by the progressive affinity of these salts for water, thus competing with the emulsion colloids.

The *alkali cations* are much less important. Their series runs rather irregularly; generally Mg $<$ NH$_4$ $<$ K $<$ Na $<$ Li (Li being most precipitant). If the electric charge of the colloid is reversed, *f. i.*, by acids, then the anion and cation series are also reversed. The *earthy metals* (Ca, and so forth), form irreversible precipitates. They also reverse the charge and therefore the effects of the anion series (Mg acts like the alkali metals). The tendency to irreversible precipitation is much greater with *metallic salts*.

Imbibition.—Plates of gelatin (glue) or other hydrophilic colloids, when laid in wate, or watery solutions, imbibe water and dissolved substance, and thus swell. Polypeptides are oriented as a lattice which enables them to enmesh large quantities of water (M. Irwin, 1925). The water is attracted and retained with considerable force, according to the affinity of the emulsoid for water. This mechanism is important in the regulation of the fluid content of the cells and tissues. The colloid must compete for the water with the other dissolved substances. The imbibition is therefore influenced by the anion series, in the usual order, iodide to chloride increasing, acetate to sulfate decreasing, the imbibition (Hofmeister, 1891). The cations have relatively little effect. OH and, still more, H ions greatly increase imbibition (Spiro, 1904; Ostwald, 1905). In agar jellies, the phenomena are exactly reversed.

Ostwald (1916) noted that the results differ according to whether dry or moist gelatin is used. Lenk (1916) found that for the salts of most monobasic anions (chlorides, and so forth) the swelling increases with the concentration; whereas with dibasic and tribasic anions (sulfates, citrates, and so on) the maximal swelling occurs with medium concentrations. According to Ehrenberg, 1913, the lyotropic series is reversed for gelatin when the concentration of the salts is low ($\Delta < 0.5$). The swelling of gelatin is also influenced by *nonelectrolytes*, decreased by sugars and glycerin, and increased by alcohol and especially urea (Pauli and Rona, 1902). The coagulability of gelatin solutions is increased by the substances which lessen swelling, and *vice versa* (Pauli, 1907).

Distribution of Salts in Imbibition.—The gelatin also takes up the solutes. Hofmeister found that the quantity taken up increases with the concentration of the solution, to a certain limit, which is reached late with the iodide end of the series, and early with the sulfate group.

SURFACE PHENOMENA

Surfaces, the planes of separation of two phases, give rise to the important phenomena of surface tension and adsorption. These are especially prominent in colloids and therefore in protoplasm, the particles of which give rise to very extensive surfaces (A. B. Macallum, 1912, 1913). They are concerned in the shape and size of the cells; in the consumption or liberation of energy (for any change in surface tension implies a corresponding change in energy); and in the distribution of solutes. Dissolved substances generally modify the molecular attraction and therefore the surface tension. In watery solutions, organic substances generally diminish, inorganic sometimes increase, the surface tension; but there is no simple general law, and the effect is not simply proportional to the concentration. *"Surface tension"* properly applies to the system of liquid:air; *"interfacial tension"* to liquid:water. They are usually, but not necessarily, parallel.

Solution-Affinity.—A substance that lowers surface tension passes more readily out of the solution and into the surface; it has a low solution-affinity or "Haft-druck" (Traube). The concentration at the interface favors the penetration of the substance through membranes and into cells, and solution-affinity is therefore an important factor in osmosis, narcosis and other pharmacologic phenomena. The concentration of solutes on surfaces is illustrated by the *adsorption of dissolved substances by powders; f. i.*, by the decolorization of potassium permanganate by filtering through sand; the adsorption of colors or alkaloids by charcoal, and so forth. Sugars are not adsorbed because they have relatively little effect on surface tension. These adsorptions are reversible; *i.e.*, the adsorbed substance may be removed by the addition of another solute which lowers surface tension more powerfully.

Adsorption is a matter of the relative affinity of the solute for the two solvents. This may be determined by the cohesive or adhesive forces that constitute surface tension, but in other instances other physical forces, such as the electric equilibrium, may come into play; others are more strictly chemical. The causes are often difficult to analyze (A. P. Mathews, 1921). The firmness of the adsorption varies greatly.

Adsorption on Chemic Reactions; Catalysis.—The surface condensation facilitates chemic reactions in accordance with the law of mass action by bringing the dissolved molecules into closer contact. Accordingly, suspension colloids, with their large surfaces, generally function as catalysts; and enzymes in general probably act largely through surface action.

OSMOSIS

Osmotic phenomena belong to the more important effects of the biochemically inactive salts and other crystalloids and of water. They occur whenever solutions of different (molecular) concentration are separated by a "*semipermeable*" membrane that permits the passage of the solvent, but which interposes an obstacle to the free diffusion of the solute. Dissolved molecules tend to distribute themselves equally throughout a solvent. If their passage is hindered by a membrane, the equality can only be obtained by the passage of the solvent from the more dilute to the more concentrated solution. The more concentrated solution therefore tends to increase in volume. If this increase is prevented (*e. g.*, if the solution is inclosed by rigid walls), a certain "*osmotic pressure*" is developed. The phenomenon is illustrated by the swelling of red blood and other cells in water; and conversely, by the shrinking of plant cells and crenation of red corpuscles in strong salt solution.

The pressure is due to the kinetic energy of the molecules that can not pass the membrane. In this, each dissociated ion acts as a molecule. Colloidal aggregates, lyophilic and lyophobic, and indeed the particles of suspended powders, such as clay, also have the same kinetic energy and exert the same osmotic pressure, per aggregate or particle (Svedberg, 1934); but as the units are larger, their number cannot be so high as that of molecules in true solutions, and their "oncotic" pressure is correspondingly smaller.

The envelopes of certain *vegetable and animal cells*, such as the *red blood corpuscles*, approach fairly closely to the definition of "semipermeable." Most cells, however, and dialyzing membranes in general, are not *absolutely* impermeable to the solutes, but offer only a partial obstacle, so that the solutes pass the membranes, but more slowly than does the solvent. Nondialyzable solutes are therefore hypertonic to those which are easily dialyzable. If a membrane separates two solutions of electrolytes, one diffusible, the other nondiffusible, differences of electric potential are created by the unequal distribution of the ions, according to *Donnan's membrane equilibrium*, that the products of the concentration of each pair of oppositely charged diffusible ions are the same on the opposite sides of the membrane.

Cell membranes of vertebrate tissues are generally freely permeable to water, H ions, and probably to NH_3; more or less to urea and dextrose, and to but few other solutes (review, J. P. Peters, 1944).

Unilateral Preferential Permeability.—Living membranes and some dead membranes may be more permeable in one direction than in the other. This is important for absorption from the intestines or through frog skin (Wertheimer). In the latter it is not conditioned on life, or on electric potential, but on different colloidal structure of the two sides of the skin membrane, so that these behave differently toward the solute (Leuthardt and Zeller, 1934). The permeability to water, however, is identical in both directions, even in intact frogs (van Hevesy *et al.*, 1935). Analogous differences are observed in collodion membranes; much less protein diffuses from the side which was away from the glass when the membrane was formed (Gaebler, 1931), owing probably to differences in the retention of solvent and speed of drying (review, R. Höber, 1936).

Calculation of Molecular Concentration and Osmotic Pressure.—Since the osmotic pressure has a definite relation to the molecular concentration, the determination of the one quantity permits the calculation of the other. The molecular concentration of a watery solution can be calculated by dividing the *depression of freezing point* of water (Δ) by 1.85; the latter is the amount of depression produced by a gram-molecule dissolved in 1 liter of water (Raoult's law). The maximal *osmotic pressure* is obtained by multiplying the molecular concentration by 22.34 atmospheres. Raoult's law holds strictly for concentrated solutions of all substances, and for dilute solutions of *nonelectrolytes*, such as the sugars, urea, glycerol, alcohol, and so forth. However, dilute solutions of *electrolytes*—salts, acids or bases—behave as if each ion acted as a molecule and show a correspondingly greater concentration than would be deduced from Raoult's law.

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OSMOTIC ACTIONS ON CELLS AND TISSUES

These consist primarily in *changes of composition*, the transfer of water and of solutes into or out of the cells. This leads to secondary effects: *Changes of water content* alter the volume and pressure, as is seen in the crenation and hemolysis of red blood cells. They may disorganize the protoplasm, as by the precipitation of globulins; and changes in *electrolyte concentration* change the electric potential. This, and the water content, alter the state of the colloids. Hypertonic and hypotonic solutions act in opposite directions as concerns volume and pressure; but the final functional results are often similar.

Molecular Concentration of the Blood and Tissues.—The total molecular concentration of living cells is probably somewhat higher than that of the body fluids. The plasma, lymph, and all other body fluids (except urine, saliva and gastric juice) of all mammals, depress the freezing point by about 0.56° C., corresponding to 0.33 mol per liter. Relatively slight departures from this are promptly injurious, and the organism resists any attempts to alter its osmotic concentration. The fluids of lower animals have a somewhat different concentration, adapted to their environment.

Human Blood.—The extreme variations of the freezing point in health are between 0.49° to 0.59° C. The molecular concentration of the blood is not altered by the quantity of fluid or salt in the food; nor by hydremia produced by hemorrhage; nor by thickening the blood by profuse diaphoresis. The intravenous injection of anisotonic solutions alters it but temporarily. About the only method of raising it permanently consists in interfering with the regulating mechanism, by seriously injuring the kidneys; then it proves fatal when the Δ approaches 0.8° C. The limits between which cells of mammals can functionate at all are comprised between Δ0.35 and 0.6 or somewhat higher. The *molecular concentration of the saliva* averages lowest of all secretions, its freezing point being normally −0.11° to −0.27° C., but if the rate of its secretion is increased, it may reach that of the blood (−0.58°).

Osmotic Equilibrium of Lower Animals.—The narrow limits of mammals are considerably extended in the lower forms of life. With *marine animals*, up to the selachians, the molecular concentration of the body fluids approaches that of sea water, and becomes independent only in the teleosteans. Dogfish are intermediate (Scott, 1913). In the marine animals, a concentration equal to that of the serum of mammals would liberate the hemoglobin. This adaptation of the osmotic resistance of cells to their normal environment is curiously developed in the small fish Fundulus, which thrives equally well in sea water and in distilled water. It is due, in this case, to a high degree of impermeability to both water and salts, so that osmotic pressure can not be developed. *Sweet-water animals* have a molecular concentration approaching that of mammals, salts being probably retained by chemical or physical affinity for the colloids. The molecular concentration of *plant juices* is also considerably higher than that of water. In the large *vacuoles of plant cells* the concentration in the internal fluid may be ten times that of the external (M. Irwin, 1925). *Fungi* often have a high resistance against osmotic changes, presumably because their envelopes are relatively impermeable. Torula, *e. g.*, can develop in a saturated solution of sodium or lithium chloride, the latter having an osmotic pressure of 2760 atmospheres (Raciborski, 1906; see also L. A. Hawkins, 1916).

Osmotic Changes in Red Blood Cells.—Hypertonic solutions produce crenation; if the solutions are hypotonic beyond a certain degree, the cells swell and lose their hemoglobin and salts. In life, these changes can be produced only by intravenous injection of anisotonic solutions.

The *resistance to osmotic hemolysis* varies in different *species*, and somewhat even with individuals. With human blood cells, laking begins in 0.48 to 0.42 per cent NaCl, and is complete in 0.38 to 0.32 per cent. The NaCl percentages for beginning and complete laking with other animals are: guinea pig, 0.420 and 0.312; dog, 0.462 and 0.330; rabbit, 0.526 and 0.385; beef begins at 0.58; horse at 0.68 (Musser and Krumbhaar, 1946; and others).

These differences refer only to hemolysis; the osmotic swelling, measured by the hematocrite, is about equal in the different species. The difference to water laking is generally inverse to that for saponin laking (Rywosch, 1907). Hemoglobin is held in the corpuscles only when all the cell proteins are in the proper colloidal condition. Changes in this, as by *p*H, metallic salts, formaldehyde, and so forth, produce shrinkage and cause hemolysis. *Increase of temperature* increases the resistance to osmotic hemolysis, owing to a change of the internal osmotic pressure (Jacobs *et al.*, 1936). *Hemolysis by hypertonic solutions* was investigated by C. C. Guthrie and Lee, 1914.

Permeability of Red Blood Cells.—These are difficultly permeable to Na, Ca and Ba ions, fats and sugars, slightly permeable to amino acids, freely permeable to all anions, ammonia, urea, alcohol, aldehydes and bile salts. The permeability is influenced by the *p*H. It increases with the Na and K ion concentration of the plasma and decreases with Ca. *Ammonium salts* lake even when added to isotonic NaCl solution. This is explained by hydrolysis with formation of the NH_3, which penetrates readily, and is followed by the osmotic attraction of water (Jacobs). The permeability to solutes is increased by saponin and other hemolytic agents. In saponin laking, increased permeability of the cell membrane can be demonstrated before the salts pass out of the cell (G. N. Stewart; Woelfel, 1908).

The permeability of the corpuscles for Na and K ions was shown by H. J. Hamburger, 1916. He also found that the addition, within physiologic limits, of CO_2 to the serum drives K ions into, and Na ions out of, the corpuscles. Fluoride and monoiodoacetate cause rapid escape of potassium from rabbits' erythrocytes (H. Davson, 1941). *Human erythrocytes* are more resistant than other species to changes of cation concentration. Placed in NaCl solution, their K decreases about 5 per cent; in KCl solution, it increases 3 to 10 per cent. The permeability increases at *p*H 8.3 to 8.8 (Maizels, 1935). If radioactive chloride, bromide or iodide is added to human blood, equilibrium is established within ten minutes, the bromide or iodide of the red cells rising higher than that of the serum (P. K. Smith *et al.*, 1941). Rohonyi and Lorant, 1916, found that *carbon dioxide* causes the erythrocytes to take up chloride from the serum, with an increase of serum alkalinity. Similar changes occur in hemolysis.

Aliphatic narcotics in anesthetic concentrations decrease the volume of blood corpuscles and decrease swelling and hemolysis by hypotonic solutions (v. Knaffl-Lenz, 1918).

The selective permeability of cell membranes varies for each class of cells, some being impermeable to one substance, some to another. In general, K enters cells fairly readily. If Na^+, Mg^{++}, Br^-, Cl^-, I^-, NO_3^- or SCN^- are injected intravenously, they are distributed exclusively through the extra cellular fluids (Winckler, Smith and Schwartz, 1939). The selective permeability is subject to changes with the functional state of the cell. It is often different in the inward and outward direction.

Permeability to Different Substances.—With most living cells, lipid-soluble substances penetrate more readily than those which are only water soluble, but the membrane is not absolutely impermeable to salts; and some substances penetrate independently of their lipoid solubility. It is generally assumed that the membrane is constructed of lipid and protein colloids, and that both play a part in the penetration. Plant cells, like red blood corpuscles, are almost impermeable to most salts and sugars, but permeable to ammonium, urea and lipolytic agents (Overton, 1895, 1899). *Striped muscle* is nearly semipermeable (similarly to a colloidin membrane in which $CaHP_2O_4$ has been deposited); *smooth muscle* is highly permeable to sugars and salts (Meigs, 1912 and 1913). Living *human skin* is permeable to cations (K > Na > Li > Ca > Mg > Al) and to anions (I > Cl > NO_3 > SO_4 > citrate > salicylate) (Poznanskaya, 1940). Excised normal *lens* behaves as an inert semipermeable membrane (review, M. C. Bourne, 1937).

Permeability for alkaloids is easily observed in plants by the precipitation of the tannin within the cells. Only the free (basic) alkaloids penetrate; the alkaloidal salts enter much more slowly, namely, in proportion as they are hydrolyzed. Their toxicity is favored by the addition of alkalis; this applies also to fish and frog larvae. Harvey, 1913, found that cell membranes are readily permeable to weakly dissociated *alkalis*, but remarkably resistant to those which are strongly dissociated.

Absorption of Dyes.—Ehrlich, 1887 and 1893, found that vital staining occurs especially with basic dyes. Overton, 1900, referred this to their lipid solubility. However, certain lipid-soluble dyes are not absorbed; while others, insoluble in fats, are nevertheless absorbable. Indeed, Asher and Gannus, 1911; Harvey, 1911; Kite, 1913; and others, found little relation. Acid dyes stain the protoplasm diffusely, while basic dyes stain mainly the cell granules.

Permeability of Internal Cytoplasm.—Kite, 1915, found that incised and punctured cells offer the same obstacles to the penetration of dyes as do intact cells. This was originally interpreted as showing that the cytoplasm itself is semipermeable; but it is now attributed to the precipitation membrane which forms rapidly when naked living protoplasm comes in contact with watery fluids. Dead protoplasm is water soluble, and therefore does not form the precipitation membrane (Seifriz, 1918). The internal protoplasm of cells is a continuous watery phase. The existence of brownian movement in living cells shows that their interior cytoplasm is liquid; but with adult cells it may become gelatinous (Chambers, 1917). With death, the protoplasm coagulates and the brownian movements are arrested. The interior of the nucleus is also chiefly liquid (R. Chambers, 1943).

Changes of Permeability in Stimulation.—The permeability of the cell membrane appears to increase suddenly at the moment of stimulation; the resulting change of surface potential is a necessary part of the stimulation phenomena.

The membranes of all animal and plant cells are *polarized*, the inner surface being negative to the external, producing the "*current of rest.*" On stimulation, the temporary increase of permeability to ions causes a wave of depolarization or negativity to pass over the external surface.

The influence of stimulation, narcotics and salts on cell permeability was pointed out by Osterhout, 1912; R. S. Lillie, 1912; J. Loeb, 1913. Stimulation decreases the electric polarization; it causes the diffusion of intracellular pigment (Lillie); the diffusion of ions from frog eggs (McClendon, 1915), and so forth. Asher observed that the vital staining of *gland cells* is greatly influenced by their functional activity, being increased by pilocarpine and diminished by atropine. *Semipermeability persists only during life.* It is lost when the cells die, so that dead cells merely imbibe solutions, like gelatin or fibrin (J. Loeb, 1913). Living tissues resist the entrance of all acids (except salicylic), while dead tissues are freely permeable to them (Harvey, 1914).

Osmotic Exchanges in the Body.—If a foreign solution is introduced—*f. i.*, into the intestines or peritoneal cavity or blood—osmosis rapidly brings its total molecular concentration to that which is normal for the tissues. This exchange could be effected either by the passage of water, or by the passage of the normal salts from the tissues into the solution. In fact, all three processes generally participate, their share varying according to the special permeability of the tissues. In general, the exchange occurs mainly in the direction which favors the *absorption*. When the molecular concentration of the blood has been reached, there remains less scope for osmotic exchanges, and further absorption occurs by other forces (filtration, imbibition, and the like), generally much more slowly. The role of osmosis in absorption is therefore important, but limited. In the *secretion* of the body fluids, *f. i.*, the urine or lymph, it is important mainly by setting limits to the real secretory forces.

The absorption of solutions from serous cavities and lymph spaces is almost entirely physical, for it occurs in dead animals, although it is more rapid when the circulation is intact, because the absorbed products are then more rapidly removed.

Frog skin transports fluid from the exterior toward the interior surface (Wertheimer). This is due partly to the different colloidal structure on the two sides (Leuthardt and Zeller, 1934), the resistance of the osmotic and electrical potential being overcome by the oxidative processes of the living cells (Adolph, 1929), probably by the combustion of pyruvic and lactic acids (Huf, 1936). Its permeability to water (or deuterium oxide) is the same in both directions (von Hevesy *et al.*, 1935).

Absorption from the alimentary canal is probably more dependent upon forces other than the osmosis than is absorption from serous cavities, but in man, for instance, hypertonic sugar solution does not leave the stomach in significant amount until its concentration has been reduced to 15 per cent; and it does not leave the duodenum until it has become isotonic (T. G. Miller, 1939).

Importance of Osmotic Exchanges in the Intestine.—Osmosis has at least a modifying influence on intestinal absorption. An isotonic condition becomes established promptly (but is not completed in the stomach; E. Otto, 1905). The changes result in corresponding alterations in the composition of the cells of the gastric and intestinal mucosa, which are therefore also subjected to osmotic salt action. This causes irritation. When the irritation is mild, it increases secretion, absorption and peristalsis. More severe grades of irritation produce emesis and inflammation. Salts not absorbable by the intestine (*cathartic salts*) are reduced to isotonic conditions by the transfer of fluid. This fluid is retained in the intestine with the salts, increasing the bulk and fluidity of the intestinal contents, and serving as a mechanical stimulus to peristalsis. This explains largely the cathartic effects of these salts.

Absorption Curve.—Hanzlik and Sollmann (1909 to 1913) found that the absorption of phenol, alcohol, iodide and presumably other substances from intestinal loops follows a similar curve, the rate being rapid for the first ten to thirty minutes, and then much slowed. Various factors seem to be concerned in this phenomenon. Brodie and Vogt, 1910, showed that the *oxygen consumption* of the intestines is increased during the absorption of normal saline, water and peptone solutions, indicating that the cells also play an active part in the process.

Absorption from Colon.—Goldschmidt *et al.*, 1919, found that diffusion occurs in both directions. With fluids below a certain threshold (about 0.16 per cent NaCl, with $\Delta 0.134$), chlorides pass from the blood into the colon. With hypertonic solutions (above $\Delta 0.786$ = NaCl 1.2 per cent), fluid at first goes into the colon. Finally, the Cl and the freezing point come into equilibrium with the blood.

Fate of Salt Solutions within the Body.—In whatever concentration and by whatever channels salts are introduced into the body, they *tend to produce hydremic plethora.* If isotonic or hypotonic solutions are introduced, they dilute the blood by their own fluid; if hypertonic solutions are injected, the blood draws fluid from the tissues until it has resumed its original concentration. *Anisotonic solutions* temporarily alter the *molecular concentration* of the plasma.

However, *the blood has a remarkable power of resuming its normal condition, its total molecular concentration, ratio of individual constituents, ratio of corpuscles to plasma, and total quantity* (*in about this order*). This process of restitution is far advanced before a quick intravenous injection can be completed; the molecular concentration returns to near normal within ten minutes; the quantity of blood and individual constituents are restored somewhat more slowly, but they are almost normal in half an hour; after two hours, the blood presents only slight abnormalities, even when large injections have been made (Magnus, 1901; Sollmann, 1901).

The *total molecular concentration* is the first factor to be restored, mainly by the passage of the dissolved molecules: if a *hypertonic solution* is injected, the injected molecules leave the blood rapidly. Other molecules leave more slowly, and water is taken up into the blood from the extracellular fluid, which becomes hypertonic and, in its turn, draws water from intracellular fluid until its volume is actually increased, the intracellular fluid becoming more hypertonic (A. W. Winkler *et al.*, 1944). When the normal molecular concentration is restored, the phenomena become identical with those following the injection of isotonic solutions. If a *hypotonic solution* is injected, the principal phenomenon at first is the passage of molecules into the blood, the injected molecules leaving the plasma slowly. The water also leaves only gradually, *i. e.*, mostly after the normal concentration has been reached; and then by the same process as with isotonic solutions. If an *isotonic solution* of a single salt (sodium chloride or sulfate) is injected, both the fluid and the injected molecules leave the circulation, the molecules somewhat more rapidly. At the same time, other molecules enter the circulation. This process continues (for about two hours), until the original quantity and composition of blood have been practically restored.

Mechanism of Restoration.—This is initiated by the rapid exchange between the blood and the extracellular and intracellular fluid, chiefly by transfer of water. It is completed by the elimination of excess fluid and solutes from the body, by the urine, sweat and, if necessary, by vomiting and diarrhea. The larger volume of the extracellular and especially of the intracellular tissue fluids enables them to take up a correspondingly larger volume of water and salts than the blood. The striated muscle cells (Wahlgren, 1909) and the liver (Sherrington and Copeman, 1893; Uschinsky, 1905) play the most important role in the rapid exchange.

Fluid Distribution in the Body.—The blood plasma amounts to about 5 per cent of the body weight; the interstitial tissue fluid to about 15 per cent; the intracellular fluid is about 50 per cent. The "*bromide space*," or "*thiocyanate space*," which corresponds approximately to the sum of the plasma and interstitial tissue fluid, amounts to about 25 per cent of the body weight in normal human subjects. The *concentration of dissolved substances* is approximately the same in the plasma and interstitial fluid (except protein); but it is quite different in the intracellular fluid. The *milliequivalents per liter of blood plasma* are: *cations*, Na, 153; K, 5; Ca, 5; Mg, 2; total, 165; *anions*, Cl, 113; HCO_3, 27; proteins, 18; others, 7; total, 165. For *intracellular fluid*, they average K, 150; Mg, 30; Na, 12; Ca, none; total, 192; protein, 80; phosphate, 70; others, 42; Cl, none; total, 192.

The quantity of material of which tissues can dispose, without visible change, is astonishingly great. In rabbits, the tissues may take up Ringer's solution amounting to four times the quantity of the blood (Bogert, Underhill and Mendel, 1916). However, very large injections give rise to ascites, effusions and diarrhea.

Conditions Delaying the Restoration of the Blood Volume.—Bogart, Underhill and Mendel, 1916, confirmed that in normal dogs and rabbits the blood volume returns to normal within half an hour after the intravenous injection of warm Ringer's fluid, equivalent to the total blood volume. This is delayed by morphine and by nephritis (uranium, chromate or tartrate), but not by ligation of the kidney vessels. The restoration is not affected by the addition of 0.4 per cent sodium carbonate, either in normal or in nephritic animals. Gelatin solutions (2 per cent) may leave the blood as rapidly as plain saline, although more commonly from 11 to 27 per cent is still present in the blood after half an hour. The gelatin leaves the blood in the same ratio as the fluid (Boycott, 1914) and is partly excreted in the urine.

Dehydration.—Reduction of the fluid of the body below the amount necessary for the normal functions may occur through deficient income or excessive loss by perspiration, diarrhea, persistent vomiting; it may be hastened experimentally by injection of hypertonic sucrose solution (Gregerson and Painter, 1939). It may also be produced by withdrawal of sodium, since there is a close relation between the volume of water and of sodium in the extracellular fluids, so that the loss of either entails decrease of the other. In the early stages of dehydration the loss of water and sodium falls chiefly on the interstitial fluid, but the plasma contributes somewhat from the start, and much more when the loss of either water or sodium exceeds a critical amount rmine, methylene blue, wyler *et al.*, 1942). merular filter holds

Lymph formation takes place chiefly by it passes egg the blood plasma through the capillary endothglomerular the tissue spaces, although other forces also play ules of (Carlson *et al.*, 1908; Boehm and Asher, 1909). This filtration depends chiefly on the balance between the hydrostatic pressure in the capillaries (35 mm. Hg toward the arterial, 13 to 14 mm. toward the venous end) and the colloidal osmotic pressure of the plasma, 25 to 35 mm., owing chiefly to the albumin. This permits normally some filtration of fluid near the arteries, especially as the plasma proteins filter to some extent, especially in the portal circulation and in inflamed capillaries (C. H. Wies and Peters, 1937). Some reabsorption would take place toward the venous side (E. M. Landis, 1934). The total normal lymph filtration in twenty-four hours has been estimated as fifty times the plasma volume. It is increased by decreasing the plasma colloids, and by increasing the plasma volume by injection of fluid, especially of hypertonic solutions. It is also increased locally by increased activity of the tissues.

Asher, 1913, pointed out that filtration can not be an important factor in the secretion of *saliva*, *sweat* and *bile*, since the secretion pressure exceeds the blood pressure. The physico-chemical conditions of salivary secretion were investigated by Japelli, 1906; those of tears and collyria by Cerrano, 1909.

Edema.—Salt action, osmosis and colloid imbibition are important factors in edema, *i. e.*, the excessive accumulation and retention of fluid and salt within and between the cells.

The edema fluid is analogous to lymph and may therefore be increased by the same agencies which increase lymph flow; hydremic plethora; lymphagogues of the "second class" (peptones, and so forth); increased blood pressure; venous obstruction; injury to the vascular endothelium, and so on. However, for the retention of fluid it is further necessary that the drainage of the lymph be obstructed, or that there be an increased affinity of the tissues (or colloids) for fluid. The cooperation of several of these factors is generally necessary for the production of noticeable edemas. Experimental edemas, resembling the clinical, require the simultaneous presence of nephritis, hydremic plethora and vascular injury (Pearce, 1909). Extensive intravenous injection of salt solutions produces ascites and edema of the internal organs, but not of the normal skin or subcutaneous tissue. To effect these, the skin must be irritated (Cohnheim and Lichtheim, 1877); or the vessels injured, as by arsenic (Magnus) or uranium.

Salts and Edema.—As intercellular fluid cannot be retained without sufficient solute to keep it isotonic, deficiency of sodium chloride tends to lessen the production of effusions, and to hasten their absorption. This is the rational basis of *the treatment of nephritic edemas by withholding salt from the food* (advocated by Widal and Javal, 1903). The treatment is not always successful (Blooker, 1909). *Edema by decrease of plasma proteins* occurs when these are reduced below 5.5 per cent (Peters and Van Slyke; Leither and McLean, 1929), as after repeated hemorrhages, and in starvation or "war edema" (Schittenhelm and Schlecht, 1919; J. B. Youmans *et al.*, 1932).

Colloids and Edema.—Martin Fischer (1908 to 1915) suggested that edema is due chiefly to changes in the affinity of the tissue colloids for water and salts, analogous to the swelling of gelatin or fibrin. This is modified to a varying degree by electrolytes, not by nonelectrolytes. It is especially increased by acids; and the production or accumulation of acid, including CO_2 in inflammation, venous stasis, and so forth, would therefore be the principal cause of edema (and the concomitant salt retention), and incidentally of nephritis. Fischer was also inclined to deny that osmosis has any part in these or other vital phenomena, and to refer to imbibition all the phenomena generally classed as osmotic; but serious objections have been raised to some of Fischer's deductions (L. J. Henderson *et al.*, 1914). *Particulate matter*, such as finely divided carbon and especially blood corpuscles and platelets, are reported to promote the flow of perfusion fluid through the finer capillaries of frogs, and thereby diminish edema (Zweifach, 1940; Danielli, 1940).

Salt Actions on Urine.—The introduction of salts or fluid into the body results in increased output of urine, *i. e.*, saline diuresis. This is largely physical, owing chiefly to the hydremic phethora which increases the renal circulation and the glomerular filtration pressure, and decreases the viscosity of the blood and the water-retaining affinity of the plasma proteins. Hypertonic solutions dehydrate and shrink the kidney cells, and thus widen the blood and urine channels. Saline dehydration also increases filtration through other colloid surfaces, *f. i.*, frog skin.

Filtration in Dead Kidneys.—Hydremic plethora and dehydration increase the ureter flow in perfused dead kidneys, in close analogy to their effects on the living kidney, except that the composition of the filtrate is that of the perfusing fluid (Sollmann, 1903 to 1905). This holds true also for heart-lung-kidney preparations when the vitality of the kidneys is suspended by cyanide (Starling and Verney, 1925). The urine flow and kidney volume of excised and *reimplanted kidneys* react the same as normal kidneys to urea, hypertonic salt solutions, and to the methylxanthines (Quinby, 1917); these, however, also change the composition of the filtrate. Such transplanted kidneys have been observed to function normally over four months (Ibreka, 1926).

Course of Saline Diuresis.—The physical element in the diuresis is especially conspicuous in the early periods of the diuresis, when the changes in the blood are relatively large, and when the rapid flow of the urine through the tubules leaves less time for the secondary, reabsorptive and secretory changes. The *degree* of diuresis (the total quantity excreted) depends largely on the quantity of solution (both of the dissolved substance and of the water) which has been introduced; but the *rate* of diuresis (the quantity excreted within a short time after injection) depends largely on the concentration of the solution, if this is given intravenously. Water, which is strongly diuretic when taken by mouth, may diminish the urine when injected by a vein. The course of the diuresis is fairly parallel to that of the changes in the renal circulation, in the case of gum saline solution; but with intravenous injection of hypertonic solutions (of sodium sulfate or urea), the diuresis considerably outlasts the circulatory changes (Cushny and Lambie, 1921); this is probably due to the persistence of slight changes in the saline composition of the blood. The *concentration of the urine* varies with the concentration of the solution which has been introduced: it may fall as low as △0.12°, or rise as high as △3.0° C. On the whole, the composition of the urine approaches the more closely to that of the blood, the faster the diuresis. In the *ordinary secretion of urine*, osmosis would be an obstacle, rather than an aid; for the molecular concentration of urine differs widely from that of the blood (△ *urine, ordinarily*, 0.9° to 2.1°; *extremes*, 0.12° to 3.0°; △ blood, 0.55° to 0.60°); and the kidney has to perform considerable labor to overcome the difference in osmotic pressure. Inability to concentrate or dilute urine is characteristic of various types of nephritis. This work does not seem to be injurious to normal kidneys, but concentration of urine may be injurious to nephritic kidneys.

The *work performed in urine formation* can not be calculated directly from the total molecular concentration, since the departure of every constituent from its concentration in the blood requires work. Barcroft and his coworkers found that the diuresis following the injection of isotonic solutions did not increase the *oxygen consumption of the kidney* and therefore presumably does not involve work; but that the oxygen consumption increases when hypertonic urines are secreted in response to sulfate injection. Caffeine diuresis also involved work. However, Hayman and Schmidt, and Fae, 1929, did not obtain increase of oxygen consumption with sulfate diuresis, unless the renal blood flow was markedly increased, so that the interpretation of the oxygen consumption is ambiguous.

Threshold and Nonthreshold Substances.—The relative concentration of the constituents of the urine differs more or less from that of the plasma. Cushny pointed out that they may be arranged into two classes: The *threshold substances*, sugar, Na^+, Cl^-, HCO_3^-, are found in the urine only if their concentration in the plasma surpasses a certain threshold level. Their urinary concentration is ordinarily not much higher than in the plasma, and may be very much lower. The *nonthreshold substances* occur in the urine whenever they are present in any quantity in the blood plasma, and their urinary concentration is much higher than in the plasma. They include urea, creatinine, ammonium, phosphate, sulfate ions, inulin and most substances not normal to the body. Uric acid and potassium are also more concentrated in the urine, but the difference is not so great. *The explanation of the classification* lies in the changes which the glomerular filtrate undergoes in passing through the tubules, where the threshold substances are reabsorbed to a large degree, the nonthreshold group little, if at all. *Diuresis* tends to increase the elimination of all the constituents, in absolute amount per unit of time. The percentage of nonthreshold substances is invariably diminished; that of the threshold substances is also often diminished, but may actually rise, according to whether they were previously above or below the concentration of the blood.

The **mechanism of urine formation,** according to the work of A. N. Richards and his associates, 1922 to 1938, consists of (1) filtration in the glomerulus of an ultrafiltrate of the plasma, containing all the nonprotein constituents of the plasma in the concentration present there. (2) Passing down the tubules, the ultrafiltrate is concentrated by the reabsorption of water, and (3) modified by the reabsorption of dextrose, NaCl and certain other salts, and (4) by the secretion of some dyes, such as phenolsulfonphthalein, and limited amounts of some other substances. Diuretic drugs may act either by increasing glomerular filtration or by decreasing tubular reabsorption. They can act on these only if there is sufficient intactness of the kidney structure, sufficient blood pressure and sufficient blood flow (J. M. Hayman, 1936).

The *evidence* of the mechanism of urine formation rests fundamentally on the application of micromethods for the direct collection and analysis of urine from individual glomeruli and tubules in frogs and necturus, by A. N. Richards and his associates, and in mammalian kidneys by A. M. Walker and Oliver, 1941.

The *glomerular fluid,* as collected from Bowman's capsule, has the composition of an ultrafiltrate of the plasma, containing all the normal constituents except proteins, in quantitatively the same concentration: chloride (Westfall, Findley and Richards, 1934), dextrose, urea, and so forth; and also foreign filtrable substances that have been injected, such as *dyes* (indigo-carmine, methylene blue, phenolsulfonphthalein). While the glomerular filter holds back the normal *proteins* of the plasma, it passes egg albumen readily. The size of the pores of the glomerular membrane is therefore between that of the molecules of serum- and egg-albumen, in man as well as in frogs. The polysaccharide *inulin* (of the molecular weight of about 50,000), which passes the filter readily and is not reabsorbed in the tubules, is especially suitable for estimating the rate of glomerular filtration. In man this averages 120 cc. per minute, regardless of the final volume of the urine proper, which may be reduced to 0.5 cc. per minute by water deprivation, or to only 15 cc. per minute in water diuresis (Richards, 1938).

Tubular Reabsorption.—The modifications in the composition of the final urine are produced in the tubules (Wearn and Richards, 1924, 1925). These reabsorb water and the "threshold solutes," which the body finds it is useful to conserve. Sucrose and xylose are also reabsorbed, but to a much smaller degree (review, J. A. Shannon, 1939). The tubules also excrete directly a minor portion of the creatinine and the major portion of some foreign substances, such as phenol red. The reabsorption is abolished if the tubules are poisoned by cyanide or by mercuric chloride, and the urine then approaches the glomerular fluid in composition (also in mammals, Starling and Verney, 1925). The *site of tubular reabsorption* has been localized by catheterization of various levels of the tubules in mammals (A. M. Walker and Oliver, 1941), as well as in frogs (A. M. Walker *et al.,* 1937). The absorption of dextrose occurs in the proximal tubules of all glomerulate kidneys; that of the other components differs somewhat in amphibians and mammals. In guinea pigs at least two-thirds of the water is reabsorbed in the proximal tubules. The chloride concentration of the fluid at this level is considerably greater than that of the plasma, probably by preferential absorption of bicarbonate. Farther along in the tubules the chloride falls, generally to less than the plasma. Concentration of the urine above the osmotic pressure of the blood plasma occurs only in animals provided with Henle loops (Starling and Verney, 1925). *Phlorhizin glycosuria* is attributed to prevention of the tubular reabsorption of dextrose (Walker and Hudson, 1937).

The tubular reabsorption of water is promoted by the pressor *posterior pituitary hormone;* that of sodium chloride by the *adrenal cortical hormone.*

The *magnitude of glomerular filtration and of tubular reabsorption* of water may be estimated in man by the injection of a substance, such as inulin, which is excreted purely by filtration in glomeruli and not reabsorbed in the tubule; or somewhat less accurately by creatinine "clearance" (Richards, 1936). These methods confirm the original estimate of Ludwig, that the volume of the glomerular filtrate is fifty to a hundred times greater than the volume of the urine as finally elaborated. This has also been shown directly by catherization of the amphibian glomeruli and tubules (Richards, 1929). This brings the reabsorption for man, per twenty-four hours, to about 25 gallons (99 liters) of water, 2 pounds (800 Gm.) of NaCl and ½ pound (200 Gm.) each of dextrose and bicarbonate (Richards, 1938).

The *mechanism of tubular reabsorption* may perhaps be explained by the assumption that the concentrated and inspissated blood which flows from the glomeruli along the tubules acts as a chemical stimulus to the tubular epithelium, causing it to absorb some substances, including water, and perhaps to secrete others, in a degree conditioned by the quantitative composition of this blood. The stimulus for any ingredient would thus operate automatically until the blood becomes normal, and cease automatically at this point. The sensation of thirst and the respiratory stimulation of acidosis are illustrations of analogous stimulation by small changes in the composition of the blood. The energy to overcome the osmotic equilibrium would be generated in the high epithelium of the tubules.

Tubular excretion appears significant only for a few substances. Phenol red, *f. i.*, is excreted to 90 or 95 per cent by the proximal tubules and only 5 to 10 per cent by the glomeruli (Richards, 1938). Diodrast, hippuran and p-amino hippuric acid (PAHA) are excreted copiously by the tubules in mammals; also uric acid in birds and reptiles. The secreting capacity of the mammalian tubules is limited, so that the secretion of one substance inhibits the secretion of the others. This has been utilized for delaying the excretion of penicillin, which appears to take this path. A similar mutual inhibition obtains for the reabsorption of dextrose and xylose (H. W. Smith *et al.*, 1938; review, J. A. Shannon, 1939). The tubular excretion of phenol red is demonstrable in *tissue cultures* of the proximal tubules of the chick mesonephros, which take the dye from the surrounding media and accumulate it in the lumen of the blind tubules. This is hindered by cyanide and inhibited by iodoacetate, the latter being restored by lactate. It appears therefore that the energy for the secretion of the dye is derived from an oxygen activation process, probably involving lactic acid (R. Chambers, Belkin and Beck, 1934).

The *aglomerular kidneys of the lower fishes* correspond in structure to the proximal convoluted tubules of the higher vertebrates. Their function was studied especially in the toad fish, Opsanus tau, by H. K. Marshall and his associates, 1929, 1934. They do not excrete dextrose, but secrete salts, urea, certain foreign substances (dyes: Hoeber, 1935) and fluid, even when the ureter pressure is raised considerably above the blood pressure. Intravenous injections of hypertonic solutions of urea, magnesium salts or sulfates produce diuresis; isotonic sodium chloride has no effect; caffeine and theophylline cause oliguria (Bieter, 1935). The evolution of the renal function and structure in fish is reviewed by H. W. Smith, 1933. The gills of fishes take the place of the kidneys to a considerable extent: By simple diffusion they excrete six to ten times more urea and ammonium than the kidneys. The less diffusible metabolites, creatine, creatinine and uric acid, are excreted chiefly by the kidneys (H. W. Smith, 1929).

Functional responses to osmotic changes consist in mild or strong stimulation, often irritative, passing into depression and finally disorganization of the cell if the changes are large. Abstraction of water from a *nerve or muscle* causes contraction; the unfertilized eggs of certain marine animals undergo parthenogenetic development, and so on (J. Loeb, 1899, 1901). If a strong salt solution is injected directly into the circulation, the main symptoms arise from the central nervous system. They consist in stimulation, with subsequent paralysis, with death from respiratory failure, presumably by dehydration of the cells of the respiratory center (A. W. Winkler *et al.*, 1944).

Local irritation by anisotonic solutions is chiefly sensory, and varies in different situations. Exposed nerves, including those in open wounds, are especially sensitive to hypertonic solutions. The mucous membrane of the mouth is insensitive to hypotonic solutions, but responds to hypertonic solutions by nausea. The mucosa of the nose is more sensitive to irritation by hypotonic solutions; so also are the conjunctiva and cornea; the latter is rendered turbid. *Eye-waters and nasal douches* should be made approximately isotonic by 1.4 per cent of sodium chloride, approximately 2 teaspoonfuls in a liter or quart of water; or by boric acid, or sodium bicarbonate, 2 to 3 per cent (4 to 5 level teaspoonfuls to a liter); or sodium borate, 4 per cent, 8 teaspoonfuls to a liter (or a fourth of these quantities to a tumbler). The *p*H is also important, 8 being best; definite irritation is produced above 9 or below 6.6 (Massart, 1889; Fantus).

Opacity of the lens results if salt is placed in the stomach of a frog. Transparency is restored if the frog is placed in water (Claude Bernard, "Anesthétiques").

Phagocytosis is decreased by small changes of the osmotic concentration of the serum, such as may occur under physiologic conditions. All anisotonic solutions are injurious, especially increased concentrations. The leukocytes recover when the normal concentration is restored. NaCl causes but little injury apart from the osmotic effect. A slight excess of calcium stimulates, while decreased activity results from a larger excess, and from reduction of calcium as by fluorides or citrates. Diminution of the normal alkalinity is deleterious, and to a less degree also an excessive alkalinity (H. Hamburger *et al.*, 1908 to 1910).

Brain Volume.—Intravenous injection of hypotonic solutions increases the bulk of the brain, and therefore the intracranial and cerebrospinal pressure. Hypertonic injections, after an initial rise, produce marked shrinkage of the brain and fall of cerebrospinal pressure. The alterations may be so great as to produce histologic changes (Weed and McKibben, 1919). Haden, 1919, introduced this means for the relief of the cerebral compression of meningitis, injecting 250 cc. of 25 per cent sterile *dextrose* solution, intravenously, two or three times a day. It was noted, however, that this reduces the cerebrospinal fluid pressure for only two or three hours, and is followed by a rise above the control pressure; this cannot be overcome by repeating the injections (E. Sachs, 1933; A. Blau, 1936), for the dextrose is deposited as glycogen, leaving the water behind, so that the blood soon becomes isotonic, and perhaps hypotonic, and the cerebral tissue swells

Sucrose does not produce this secondary rise, since it is not transformed and therefore remains hypertonic. It also causes more profuse diuresis, which eliminates further fluid. It is injected intravenously as 100 cc. of the 50 per cent solution, at the rate of 5 cc. per minute. This lowers the cerebrospinal pressure for five to eight hours, without after-rise. It may be repeated three to five times as needed (Bullock, Gregerson and Kinney, 1935; Hahn, Ramsey and Kohlstaedt, 1937). Intravenous injection of *water*, in large quantity, has little effect on the cerebrospinal fluid pressure or on the water content of the brain (Biancalana, 1930).

Intravenous Hypertonic Injection on Blood Pressure.—Injections of 10 per cent NaCl or 50 per cent dextrose or ten times concentrated Ringer solution, into the femoral vein of dogs, at the rate of 2 cc. per Kg. of body weight, cause immediate temporary fall of blood pressure, with increased heart rate and pulse pressure. The fall occurs even when the spinal cord has been pithed, so that it is apparently due to a direct vasodilator action (A. Bernstein, 1930). The plasma volume is well maintained, and the pressure and renal function are soon restored (A. W. Winkler *et al.*, 1944). Stewart and Rogoff, 1919, found *epinephrine output* markedly increased by the intravenous injection of small amounts of concentrated sodium carbonate solution. They attribute this to osmotic stimulation of the bulbospinal centers. Clinically, hypertonic injections cause a sensation of heat, sometimes with brief pain. Strongly hypertonic solutions are injected into varicose veins to produce obliterative phlebitis and thrombosis. The intravenous injection of 50 per cent dextrose is reported to shorten the bleeding time (H. Opitz, 1932).

Osmotic Effects on Heart.—In the perfused *turtle heart*, hypotonic solutions increase the tonus and the height of the contractions, shorten the A-V interval, but slow the rate. Hypertonic solutions produce the opposite effects (Goto, 1916). The isolated auricle of frogs responds similarly. Hypertonic dextrose is less depressant than NaCl. Hypertonic solutions also cause disappearance of the striations, which reappear in isotonic solution (Granemitzky, 1937).

Response of Muscles and Nerves to Osmotic Changes.—All forms of muscle, striped, cardiac and especially smooth, are stimulated by moderately hypotonic, and depressed by hypertonic, solutions. *Nerve trunks*, on the other hand, are stimulated by hypertonic and depressed by hypotonic media (Ishikawa, 1912). *Skeletal muscle* goes into contracture on immersion in *hypertonic* solutions, Ringer's, NaCl or dextrose. *Hypotonic* solutions produce twitching, contracture and rigor ("water rigor"), with accumulation of lactic acid, which may be the immediate cause of the contraction.

Osmotic Response of Uterus.—Marked stimulation occurs with even slight hypotonicity (Dale, 1912; Goto, 1916; Voegtlin and Lake, 1917); the depression by hypertonicity can be evoked even by oral administration in intact animals (Barbour and Rappoport, 1922). Hypotonicity also increases and hypertonicity depresses the response to anaphylactic stimulation (Dale, 1912).

Osmotic Response of Intestines.—The tonus and excitability are increased by hypotonic solutions, in living animals as well as in excised intestines. Hypertonic solutions depress, after a brief stimulation. This tends to expel the hypertonic solution from the lumen before it can become depressant, so that the practical effect in living animals may appear entirely stimulating (v. Oettingen and Sollmann, 1926).

The *gastric motility* is increased by hypertonic NaCl, even on intravenous injection, causing strong peristalsis of the stomach, with spastic closure of the pylorus and sometimes of the antrum (Jonkees, 1934). Oral administration of hypertonic salt or sugar solutions delays the emptying of the stomach (Gershon-Cohen *et al.*, 1938); 3 to 4 per cent NaCl provokes emesis.

Thirst is felt promptly after intravenous injection of hypertonic NaCl solution. It does not go strictly parallel to the increased osmotic concentration of the plasma. Decreased flow of saliva is a factor. The thirst may be temporarily suppressed by the injection of pitressin (J. H. Holmes and Gregerson, 1939).

Drinking of sea water is a common cause of death in men adrift on the ocean. The effects are due to hypertonicity, since large amounts are tolerated if they are sufficiently diluted with fresh water. The excess of salt does not go into the cells, but draws water from them into the extracellular fluid, producing progressive intracellular dehydration, while the volume of the extracellular fluid is not decreased. Various nervous disturbances set in shortly before death, including tremors, hyperactive reflexes, motor incoordination, and finally irregularity and arrest of respiration. The circulation functions well until the end, the plasma volume is not decreased, and renal function remains active (J. R. Elkinton and Winkler, 1944).

The functions of electrolytes in salt actions involve several factors. Aside from being the most important substances in maintaining the normal osmotic concentration, they are indispensable to cell function by regulating the electrical potential of the colloids and through this the aggregation of the colloids, their water affinity and the permeability of the surface membranes. In addition, reactive ions may enter into ordinary chemical reactions, but these are beyond the scope of "salt actions."

Importance of Electrolytes.—Muscles soon lose their excitability completely in solutions of nonelectrolytes; but this returns when they are replaced in saline solutions. A medium containing electrolytes is therefore essential to muscular contraction. The different ions are not equally effective. The nature of the cations is more important than that of the anions.

The ions arrange themselves in the usual lyotropic series, the Na and I end being the most favorable, and the K and citrate end the most unfavorable to striped muscle, and to the rhythm of the heart. With smooth muscle, on the other hand, moderate concentrations of potassium increase the tonus and the peristaltic contractions (uterus, Tate and Clark, 1921). Potassium also stimulates the tonus waves of turtle's auricle. Calcium is generally antagonistic to the effects of potassium, on all forms of muscle.

There is usually an *optimal concentration and ratio* of ions for a given set of conditions, so that addition or withdrawal has contradictory effects according to whether they lead toward or away from the optimum. Immersion in any *solution of a single salt* also renders muscle inexcitable, but with different rapidity. These differences follow the lyotropic series in the same sense.

Surface Actions of Electrolytes.—There are reasons for believing that the ion actions may be exerted only on the surface of the cells, especially by altering the permeability of the plasma membrane. The high resistance of cells to the penetration of ions makes internal effects improbable. The promptness with which the effects can be removed by the addition of a second salt also speaks against absorption. It is probable that the single salt solutions disturb the semipermeability of the membrane (J. Loeb, 1905, 1914), thus interfering with the maintenance of the electric potential which determines irritability. Cells denuded of their plasma membranes undergo complete disintegration. Calcium tends to produce coagulation of the disintegrating material where the plasma membrane has been punctured, and so repair the injury (R. Chambers, 1943). The *intracellular cations* are chiefly K and Mn; the anions are chiefly various phosphorus compounds (O. H. Lowry, 1943). Histological localization of ions by precipitating reactions is misleading, since the precipitates tend to prevent penetration of the reagent (G. H. Scott and Packer, 1939).

The practical importance of general electrolyte actions in disease and treatment is limited perhaps because their biological importance is so great that alterations of the normal are not easily maintained, being resisted by rapid passage out of the blood into inactive storage systems and by elimination. The more important disturbances of ion balance in disease are the calcium deficiency of parathyroid tetany, and the sodium deficiency of pernicious vomiting, cholera, sweating and Addison's disease. Important examples in toxicology are the disionization of calcium by citrate and oxalate, and the circulatory disturbances of intravenous injection of potassium salts.

Balanced Salt Ratios.—A solution containing a single electrolyte, no matter what the chemic nature of the latter, is fatal to all forms of life. The toxicity can be greatly lessened by the addition of a second salt. This is called the *"antitoxic action" of ions.* For perfect functionation, several salts are necessary, in a definite "balanced" ratio (J. Loeb, 1900). Departures from this ratio modify the function of the cell; larger changes are fatal.

The optimal ratios differ for various tissues, and indeed for different functions of the same tissue; for instance, a small quantity of magnesium added to Ringer's solution bathing excised intestines decreases the tonus and the height of the contractions, but prolongs the life of the preparation. Very small quantities of a second electrolyte may suffice for antagonism: the addition of $\frac{1}{4000}$ m. $CaCl_2$ neutralizes the toxic action of $\frac{5}{8}$ m. NaCl on Fundulus ova (J. Loeb, 1901, 1911). The antagonism is mutual, at least to some extent.

Even when the antagonism of two salts is at its best, it is never perfect; it requires the addition of one or more further salts to enable the cell to perform its functions properly. Indeed, *a strictly normal condition is not reached until the cell is placed in a solution, the cations of which are within narrow limits the same, qualitatively and quantitatively, as those of its normal surroundings.*

The *magnesium and calcium antagonism* presents special features. Increase of either Ca or Mg ions depresses muscle and nervous structures. Nevertheless, the effects of the Mg may be removed by addition of Ca. Ca also antagonizes the inhibitory effects of K, as well as the stimulated effects of Na (Meltzer and Auer, 1908). Strontium does not take the place of Ca in these reactions. Even more complex relations were discovered (Joseph and Meltzer, 1914).

Ions Essential to Life.—The bulk of the electrolytes of animals are made up of the cations Na, K, Ca and Mg, and the anions Cl, HCO_3, PO_4 and SO_4. All these are indispensable to animals; Na and Cl are not necessary to plants. Small amounts of iodine, Fe, Cu, Co, Zn and other metals, and perhaps many other chemical elements are also more or less indispensable, but not necessarily in the form of electrolytes. Plants require boron and manganese, copper and zinc, in field crops as well as in cultures. These *"trace elements"* form part of the essential *electron-transfer enzyme systems;* Mn in arginase, Zn in carbonic anhydrase, Al in succino-oxidase, Mg in phosphatase and carboxylase, Fe in cytochrome oxidase (review, O. Baudisch, 1943; M. E. Shils and McCollum, 1942). Excess quantities are toxic, and the margin is often narrow (review, Hoagland, 1940).

"Physiologic" or "Normal" Saline Solutions (Artificial Serums).—The deleterious effects of single-salt solutions led to the introduction of solutions better adjusted to physiologic requirements. These balanced solutions are necessary when experimenting on excised tissues. They are less important for injections into living animals, in which even single-salt solutions are rapidly adjusted by exchange with the tissues. The solutions have been devised partly empirically, partly by imitating the salts of the blood serum or sea water. Different tissues may require modifications to secure the optimal effects. The following are the most important:

Isotonic NaCl Solutions.—Nasse, 1869, determined experimentally that 0.6 per cent is the best concentration for preserving the irritability of *frog's* tissues. Later, it was shown that this solution was not indifferent: Kronecker and Stirling observed stoppage of the heart; Ringer, twitching of muscles; Locke, contractures and increased irritability; Carslaw and Locke, curare action, and so forth. These effects can be overcome by balancing the solution with other salts. However, the solution is practically isotonic with frog's blood, and therefore obviates osmotic changes. On the other hand, it is hypotonic to *mammalian blood*, which requires about 0.9 per cent NaCl. Solutions of 0.8 to 0.9 per cent are therefore generally preferred for mammals. The concentration of the U.S.P. is 0.85 per cent. Abel, however, found in vividiffusion that a lower concentration, about 0.6 per cent, prevented edema more effectively.

KCl, 0.01 to 0.04 per cent. The lower the concentration, the higher the rhythmicity.

$CaCl_2$, 0.01 to 0.26 per cent of the anhydrous salt. The concentration is adjusted to balance the potassium. "Crystals" of calcium chloride contain varying proportions of water, so that their molecular formula should be stated.

$MgCl_2$ (0.01 per cent) is added to a few solutions, especially those intended for excised intestines. It depresses the rhythmicity and so prolongs survival.

Buffer alkali is secured by sodium bicarbonate, 0.003 to 0.15 per cent, sometimes with the addition of the sodium phosphates, although these are likely to precipitate the calcium.

Dextrose, 0.1 to 0.15 per cent, is added for the more active muscles as nutrient.

TABLE OF COMMONLY USED BALANCED SOLUTIONS

Percentages

Author	Adapted to	NaCl	KCl	$CaCl_2$ (Anhydrous)	$NaHCO_3$	Other Ingredients
Ringer	Frogs	0.6	0.0075	0.01	0.01	
Howell	Frogs	0.7	0.03	0.026	0.003	
Clark	Frogs	0.7	0.014	0.012 (dried)	0.02	
Locke	Mammals	0.92	0.042	0.018	0.15	Dextrose, 0.1
Tyrode	Mammals	0.8	0.02	0.01	0.1	$MgCl_2$, 0.01 NaH_2PO_4, 0.005 Glucose, 0.1

In making solutions containing $NaHCO_3$, this must be completely dissolved before the $CaCl_2$ is added.

Balanced Solutions.—The ideal solution for maintaining the functions of excised tissues should presumably reproduce the ion ratio of blood plasma. This cannot be deduced accurately from the serum ash, since the degree of ionization in the plasma is problematical, particularly as regards calcium. The formulas in actual use represent modifications of the ash ratio that have been found practically useful. They embody the following features (the number referring to the *anhydrous* constituents):

NaCl, 0.6 to 0.7 per cent for frogs, 0.6 to 0.92 per cent for mammals. The lower concentrations are more stimulant; this means better functionation, but shorter survival of the excised tissue. The same contrast between functionation and duration of survival applies to the other ingredients.

Aeration assists both functionation and survival.

The above table gives the actual composition of the more commonly used solutions. The Howell solution may be recommended for frogs and turtles, the Locke solution for mammals.

Locke's solution is intended to be used with a stream of oxygen. It was originally devised for the mammalian heart, but it also maintains the vitality of nervous and other tissues (Hedon and Fleig, 1905). Herlitska, 1910, found the addition of *urea* and glycerin to Locke's solution essential for the excitability of the nervous system of frogs. Bombiani, 1913, found that the favorable effect of urea on the selachian heart is not shared by related substances and therefore considered it chemic. It dilates the perfused vessels of the frog (Hooker, 1911).

Cations in Human Serum.—A. B. Macallum, 1926, obtained the following percentages, which for convenience are also expressed as the chlorides:

	Na	K	Ca	Mg
Cations	0.30 to 0.31	0.020 to 0.022	0.008 to 0.011	0.0018 to 0.0034
Chlorides	0.76 to 0.80	0.038 to 0.42	0.022 to 0.030	0.007 to 0.014

Sea water has three to four times the molecular concentration of the mammalian plasma. The ratio of Na to K is approximately that of the Locke solution, but its Ca and especially the Mg are notably higher. The composition varies somewhat in different oceans; that of the English Channel may be taken as representative, with the following percentages of its principal salts: NaCl, 2.7; KCl, 0.075; $MgCl_2$, 0.37; $MgSO_4$, 0.23; CaSO, 0.14.

American analyses are furnished by Wheeler, J. Am. Chem. Soc., *32:* 646, 1910.

The freezing point of sea water is: −2.29° C. at Naples (Bottazzi, 1897); −1.90° at Pacific Grove, California; and −1.82° at Wood's Hole, Massachusetts (Garrey, 1905). Intravenous injection of sea water is more toxic to rabbits than is sodium chloride in the same concentration (A. Rabbeno, 1929). A. B. Macallum, 1910, suggested the interesting theory that the composition of the blood is a survival of the evolutionary adaptation of animals to their original marine environment.

Ion Actions on Special Tissues and Organs.—Nerve fibers lose their irritability in solutions of nonelectrolytes, and recover in salts. The cation series is similar for muscle, but the anion series is reversed. The *reaction of motor nerves to electrolytes* is an additive function of the two ions: the anions (alkalis or increase of valency) stimulate the sciatic nerve of the frog, while cations (acids) lower its irritability (A. P. Mathews, 1902). This agrees with the old observation of Galvani (confirmed by Grandis, 1902), that the nerve is stimulated when it is charged by induction with negative electricity, and depressed by a positive charge. The *oxygen consumption* of isolated frog sciatic nerve is decreased by KCl, increased or unchanged by $CaCl_2$ (Kaganovskaia and Shlykova, 1935).

Skeletal muscle, immersed in isotonic solutions of various electrolytes, may lengthen or shorten; the excitability may be diminished or increased; spontaneous rhythmic contractions may appear; or the muscle may develop "contact irritability" so that it will react to stimuli which are ordinarily ineffective. Invertebrate and mammalian muscles exhibit similar phenomena if proper conditions are maintained. *Rhythmic contractions of skeletal muscle* generally develop before the irritability is lost, when muscle is immersed in solutions of a single electrolyte (Loeb, 1899). If a certain proportion of a calcium salt is added, the rhythmic property disappears again. Rhythmic contractibility is inherent in all muscular tissues. The reason why the contraction of the heart is ordinarily rhythmic, and that of skeletal muscle not, is that the ions in the heart are balanced so as to favor rhythmic contractions, and in the skeletal muscle they are not so balanced.

Muscle electrolytes are reviewed by W. O. Fenn, 1936.

Ciliary and Muscular Movement.—R. S. Lillie (1902) studied the effects of ions on the larvae of a sea worm (Arenicola), which executes both ciliary and muscular movements. The presence of magnesium in the mixture favors the contraction of the cilia, calcium of the muscles; potassium hinders both. Parker (1905) found that potassium reverses the stroke of certain cilia.

Injection of isotonic saline solution into a serous cavity is an effective method of securing emigration of leukocytes (D. R. Coman, 1939).

Ion actions on heart are highly important for the cardiac contractions. The excised hearts of cold-blooded animals soon stop their beat when immersed in solutions of nonelectrolytes (Carlson); but they continue to contract rhythmically for a long time in certain salt solutions. Analogous phenomena are observed in the perfusion of mammalian hearts. The solutions must contain Na, K and Ca ions; and these must be in a fairly definite "balanced" ratio, as in Ringer's or Locke's solutions or their modifications. Deficiency or excess of these ions causes derangement of function; both are equally fatal. For moderate changes, the ratio is much more important than the absolute quantity of the ions. The anions are relatively indifferent. The *effects of the individual cations on the heart* are complex and rather confusing, because the response of each is modified by the presence of other cations. There are also marked but generally only quantitative differences between the different portions of the heart. *In living animals,* departures from the normal ion ratio can not be maintained sufficiently long to be of practical importance (Schafir, 1915) or even to be conveniently investigated.

Perfused hearts respond to changes of the ion ratio of the Ringer's solution according to the direction of the K:Ca ratio, practically regardless of whether the ratio is changed by increasing the one ion or by decreasing the other. The K or Ca predominance becomes conspicuous when the percentage of the one is about three or four times that of the other (Boehm, 1914).

Functions of the individual ions may be studied in segments from the various regions of the *turtle's heart.* These do not beat rhythmically in solutions of the nonelectrolytes, but do so only if NaCl or other appropriate sodium salts are added. Sodium is therefore indispensable to the rhythmicity. The addition of Ca does not appear to be especially important for the rhythmicity, but rather to antagonize the eventual toxicity of Na and of K. The addition of potassium has a marked inhibitory effect on the rhythm, which is much more marked for the cardiac muscle proper than for the nodal tissue, and may therefore be important chiefly for subjecting the cardiac muscle to the control of the normal pacemaker (Chu and Sollmann, 1925). Localized application of KCl solution, on filter paper, to the sinus of mammals shifts the pacemaking function to lower regions (B. Kisch, 1927).

Increase of the K:Ca Ratio, i. e., Potassium Excess or Calcium Deficiency.—The effects resemble those of vagus stimulation; *i. e.*, weakening of the contractions and decrease of the rhythmicity, resulting in heart block, intermissions and arrest; and in synergism with the parasympathetic stimulants (acetylcholine, and the like) and mutual antagonism with sympathetic stimulation, through the accelerator nerve or by epinephrine; and with the muscular stimulations, *i. e.*, the digitalis group. Contradictory results are reported as to the excitability of the vagus trunk. The resistance to potassium increases with the inherent rhythmicity of the cardiac tissue, in order of: sinus (most resistant), ventricle base, ventricle apex and auricular muscle (least resistant). The percentage of potassium in normal blood tends to inhibit spontaneous ventricular and auricular rhythm, and therefore renders the heart muscle more amenable to the pacemaking function of the nodal tissue.

Increase of the Ca:K ratio, i. e., calcium excess or potassium deficiency, has essentially the opposite effects, resembling both accelerator stimulation with epinephrine, and muscular stimulation with digitalis. The contractions are strengthened and often quickened, with a systolic tendency which increases to prolongation and fusion of the systoles, and culminates in systolic arrest. Calcium excess is synergistic with accelerator stimulation by epinephrine and with the systolic effects of digitalis. It is antagonistic to vagus stimulation and to the parasympathetic stimulants and may apparently cause these to produce abnormal effects.

Hydrogen-Ions on Heart.—In the perfused turtle heart, increase of alkalinity (to *p*H 7.8) increases the tonus and rather decreases the amplitude; decrease of alkalinity (to *p*H 7.3) increases the output by lowering the tonus, thus permitting greater distention and excursions (Andrus, 1918).

Abnormal ions were studied, *e. g.*, by Lussano, 1913, by modifying the constituents of Ringer's solution. Sr and Ba can not replace Ca, but their effects correspond to those of excessive Ca. Li is not toxic, but causes some osmotic slowing; NH_4 slows, but increases, the irritability and strength. The effects of lithium, and so forth, on turtle heart strips were studied by Lingle, 1902.

Radioactive Metals.—Zwaaredemaker, 1918, claimed that the potassium in Ringer's fluid may be replaced by any radioactive elements in equi-radioactive proportions. A. J. Clark, 1920, failed to confirm this generalization.

Nonelectrolytes, urea, dextrose or saccharose replacing isotonic equivalents of NaCl in Ringer's solution, behave similarly to Ca, and are antagonistic to Na and to K (Mita, 1926).

Cardiovascular effects of cations as they occur in dogs on slow intravenous infusion of single salts are described by Winkler *et al.*, 1940: *Potassium* produces intraventricular block and diastolic arrest. *Calcium* produces vagal bradycardia, ventricular arrythmias and ventricular fibrillation. *Magnesium* produces vasodilatation with fall of blood pressure. The heart is affected only with doses that cause respiratory arrest.

Blood vessels perfused with modified Ringer's solutions give somewhat inconstant results, but they are generally *dilated* by excess of Na or absence of Ca; and *constricted* by excess of Ca or of K and also by absence of K (Gramenitzki, 1927; Yamada and Yoshida, 1927). Lack of Ca and excess of Na increase the constrictor *response to epinephrine*, and this is diminished by excess of K. It persists eight times as long if dextrose is added to Ringer's solution (Hatcher, 1906). The tonus is raised by replacing the Cl with other haloid *anions*, F > I > Br (Prochnow, 1911).

The *coronary vessels of dogs*, perfused with heparinized blood, are dilated by the addition of Na and Ca in all concentrations. Dilatation also occurs if a small quantity of K is added, but larger amounts constrict, sometimes to complete coronary occlusion (Katz and Lindner, 1938).

Smooth muscle gives inconstant and contradictory results. In general, increase of Na increases the amplitude of rhythmic contractions but has little effect on tonus. Increase of the Ca:K ratio increases tone and rate, but depresses amplitude; increase of K:Ca increases the amplitude.

Details for excised intestines are reported by Whitehead, 1929; for *uterus* by Turold, 1922; for *iris* by Regniers, 1926. *Anions* arrange themselves according to the Hofmeister lyotropic series, the rhythmicity increasing in sequence from citrate to sulfate, chloride, iodide and thiocyanate (Gellhorn and Moldavsky, 1934).

Central Nervous System.—With perfusion of the *medulla* of dogs, increase of Ca:K stimulates, and increase of K:Ca inhibits response (Hooker, 1915). The perfused *central nervous system of mammals* preserves its activity best with a solution of 0.9 per cent NaCl and 0.05 per cent $CaCl_2$. These can not be replaced by related cations. Even traces of potassium are harmful (P. Gerlach, 1914). With perfusion of the *respiratory center of frogs*, increase or omission of K from balanced solutions produces depression; decrease of K causes stimulation. With Ca, increase and omission produce stimulation; diminution, depression (Hooker, 1913). The perfused *spinal cord* of frogs gave similar results (Hooker and Reese, 1914). As to the perfusion of the *medullary cardiac centers*, predominance of K stimulates the vagus and inhibits the accelerator; predominance of Ca stimulates the accelerator (Hooker, 1915).

Ion Effects on the Kidneys.—The polyuria and glycosuria which follow the intravenous injection of large quantities of most sodium salts are arrested by adding a small proportion of $CaCl_2$ (W. H. Fischer and O. H. Brown, 1903). Sr or Ba salts prevent the *glycosuria* without affecting the polyuria. Calcium also hinders the filtration of urine and impedes the circulation in excised kidneys, while magnesium favors them. The effects of most others ions investigated in this manner are referable to osmotic changes, due to differences of penetrability (Sollmann, 1905).

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WATER

Direct application of water to semipermeable cells produces osmotic changes. If the semipermeability is imperfect or impaired, there results a leaching-out of salts and, with this, a disturbance of the ion ratio. Instances of these deleterious actions are the water laking of blood and the swelling and water rigor of muscle. The surfaces normally exposed to contact with water are protected against these actions, either by impermeability, as the skin and bladder, or by the rapid passage of salts into the water, as in the alimentary tract. Even in these situations, however, the water causes more or less swelling, stimulation or irritation of the cells. Water constitutes about two-thirds of the body weight (65 per cent for dogs, 70 for macacus monkeys, 75 for rabbits; H. E. Harrison *et al.*, 1936). It is 75 to 90 per cent of the active tissues, 40 per cent of bones. The water content of the tissues decreases with age, both before and after birth. About a fourth of the available water is normally in the skin and muscles, the skin being the most flexible depot, chiefly by its interstitial fluid (L. J. Flemister, 1942).

Water is constantly lost to the body by the urine, lungs, perspiration and feces, but before this reaches a demonstrable degree of drying and concentration of the tissues, the sensation of thirst prompts the replacement of the water. Absorption of fluid, however, from the alimentary canal is not an effective protection to the water and salt content of the body, for it does not cease when this normal level is exceeded (J. P. Peters, 1944). Excess water is promptly eliminated by the excretions, which are correspondingly increased and diluted, but there is a temporary increase of the water content of the fluids and cells of the body; removal of their salts; and alterations in the proportions of their ions. These changes in turn produce functional phenomena, characterized especially by increased secretions, and by changes in metabolism. The effects vary according to whether the quantity of water is normal or excessive, and according to the channel by which it is introduced.

Water Capital and Turnover.—The tissues of an adult man contain about 40 Kg. (10 gallons) of water. Its daily turnover is by far the largest of all components of the body. From $3\frac{1}{3}$ to 10 liters, $\frac{1}{12}$ to $\frac{1}{4}$ of the total water of the body, are eliminated and must be replaced every day.

The sources of water income are food and drink, about equally (Maddock and Coller, 1937). The amount drunk as *fluids* is 800 to 2000 cc. per day. It is the most easily adjusted source, and is regulated by the thirst, according to the other sources of income and to balance the elimination. The *food* contains considerable water, averaging about 70 per cent; additional water is formed by its oxidation. From both sources, each gram of "solid" food furnishes about 0.9 Gm. of water, amounting to 1000 to 1500 cc. per day. Even in starvation, up to 500 cc. become available by oxidation of the tissues.

The *quantity of water formed by oxidation* of food materials, in terms of cubic centimeters of water per 100 Gm. of dry food, amounts to 90 to 100 cc. for fat, 50 to 60 cc. for starch, 40 to 50 cc. for proteins. Alcohol forms 117.4 cc. The oxidation of mixed food of 3000 calories furnishes about 360 cc. of water. *In starvation*, dogs drink only about half the normal quantity of water, bringing their total water intake down to $\frac{1}{5}$ to $\frac{1}{3}$ (Kleitman, 1927).

Absorption from Alimentary Canal.—Water is rather slowly absorbed from the *stomach*, where it also delays absorption of other substances. It passes rapidly, however, into the duodenum, and is absorbed readily from the *intestines*, small and large. In addition to the ingested fluid, from 3 to 5 or even 10 liters, about 2 gallons, of fluid are poured daily into the upper half of the alimentary canal as digestive secretions, and less than 150 cc. are normally lost with the stools, the remainder being reabsorbed (Maddock and Coller, 1937). In health, the absorption of ingested water occurs chiefly in the upper portions of the small intestines (von Mering, 1893; Moritz, 1893). The contents are still fluid, however, at the lower end of the ileum, with 92 to 97 per cent of water (ileocecal fistula, human; Landt and Daum, 1933). The further concentration to the consistency of the feces, which contain about 75 per cent of water, occurs chiefly in the cecum and rectum, very little in the colon proper, for man and dogs (Steggerda, 1933, 1935). With guinea pigs, water absorption takes place chiefly from the proximal colon (W. Straub and Lee, 1933).

Absorption by the Skin.—Water is not appreciably absorbed through the normal skin, although it is slowly absorbed into the epithelium and produces swelling of the epidermis. Bathing in cold water contracts the cutaneous vessels, and diminishes the loss of water by perspiration; hot water increases the loss by favoring diaphoresis.

The **excretion of water** occurs by the kidneys, skin, lungs and intestines (feces). The relative importance of these channels varies with conditions. At rest, in temperate climate, the ratio averages about 6:2:2:1; but if water is taken hot, so as to favor dilatation of the cutaneous vessels, it acts as a *diaphoretic.* Excessive quantities of water may also be excreted by the *intestine* and lead to diarrhea. Normally, however, the kidneys have the chief part in maintaining the volume and composition of the body fluid.

The *range of minimal and liberal water loss* for adult man is given in the review of T. F. Adolph, 1933, as follows: Urine, 600 to 2000 cc.; feces, 50 to 200; insensible perspiration, 350 to 700; sweat, 50 to 4000; pulmonary ventilation, 300 to ?; milk, 0 to 900.

Elimination by the skin, especially by sweating, is the widest variable in water excretion and may be much greater than is generally recognized; but it is used for heat regulation rather than for water regulation. It increases when the external temperature or the internal heat production rises. In contrast to the renal water output, it is but little affected by the amount of water available. It is the chief element in *quick reduction of body weight* by hot baths and exercise.

F. G. Benedict, 1931, cites a football player who lost 14 pounds during a hot afternoon. The total dry tissue burned was only ½ pound, so that practically 98 per cent was lost as water, mostly through perspiration.

Water Lost by Evaporation.—Under conditions of comfort, at rest and with normal basal metabolism, about 25 per cent of the body heat is dissipated by evaporation from the skin and lungs of 1000 to 1500 cc. of water per day (Wiley and Newburgh, 1931). It may amount to 60 Gm. per hour, even in sleep (G. E. Wilson, 1933). It rises to 1500 to 2500 cc. in fever (Maddock and Coller, 1937). Dehydration by more than 6 per cent of the total body water lowers the loss by evaporation (J. F. Hall and McClure, 1936).

Cutaneous elimination of water occurs by the secretion of sweat, *sensible perspiration;* and evaporation from the epidermis, *insensible perspiration.* Both are regulated by the amount of blood circulating in the skin (J. D. Hardy and Soderstrom, 1938), but they do not necessarily go parallel. Dry heat increases both; moist heat increases sweating, but diminishes evaporation and therefore insensible perspiration (Vasti, 1932). Exercise increases the sensible perspiration much more than the insensible perspiration.

The *insensible perspiration* emerges as a watery vapor, not as fluid, and does not contain solutes. It averages 200 to 400 cc. per square meter of skin per day, more for the arms and legs than for the trunk (Adolph, 1933). Its total may rise to 50 cc. per hour. It is not increased significantly by ingestion of water or normal saline solution, but is markedly increased by ingestion of sucrose, which raises the cutaneous temperature. Injection of posterior pituitary solution along with water ingestion tends to increase the insensible perspiration (Hall and McClure, 1936).

The *pulmonary water excretion* comprises the evaporation of water from the alveoli and respiratory mucosae. It depends on the unsaturation of the inspired air and on the air movement, panting being more effective than deep respiration. It is important for furred animals, but relatively unimportant for man, averaging 300 cc. per day under basal conditions (Adolph, 1933). It increases with pulmonary ventilation and therefore with exertion and fever.

In small animals, the extrarenal loss of water, chiefly respiratory, often equals the urinary output: In a rat at room temperature it amounted to 1.25 Gm. per 100 Gm. of body weight per hour; in a rabbit, to 0.3 Gm.; in man, to 0.04 Gm. (H. Heller and Smith, 1932).

The **urinary excretion of water** varies with the excess of water in the body, chiefly by diminished reabsorption from the urinary tubules, probably involving inhibition of the output of posterior pituitary hormone. The depression of freezing point of the urine therefore falls, and may be as low as −0.12° C., less than a fifth of that of the blood. When the water is absorbed from the alimentary tract, the diuresis is prompt, strong and certain so long as the kidneys are normal. If more than the customary amount of water is ingested, an approximately equal amount is usually excreted in two or three hours, in addition to the customary excretion. The capacity of urinary water output is normally large, to 10 liters or more per day, but has limits. One extreme is seen in diabetes insipidus, the other in nephritis and after posterior pituitary injection. Other forms of nephritis are characterized by inability to concentrate the urine; or both may coexist.

High Water Consumption.—Three to 5 and even 10 liters may be taken and absorbed in the day, in man, with out altering the consistence of the feces. If a large quantity is ingested, a half to three-fourths may be excreted by the urine within forty-five to ninety minutes (Mattill and Hawk, 1911). With moderately large volumes of water, 1 to 1.5 liters, diuresis does not begin until some time after detectable reduction of the salt level of the serum (review, J. P. Peters, 1944). The excretion may be forced above 10 liters per day, and continued for several weeks, apparently without deleterious effects to the kidneys or otherwise; this does not even create salt hunger (Sollmann and Hoffmann, 1905). With adequate diet and a constant NaCl intake of 16.5 Gm. daily, Kunstmann, 1933, found that 7 to 18 liters of tap water daily for eighteen weeks did not impair the kidney functions, or cause any significant change in the osmotic pressure or Cl content of the blood, nor in the nitrogen excretion. Severe thirst developed, and persisted after the high water intake was concluded. The diuretic action of moderate quantities of water can be enhanced by the addition of other diuretics, but if large quantities of water are given, the addition of diuretics has no further effect.

Composition of the Urine.—The urine in water diuresis becomes very dilute, although the total or daily excretion of the dissolved constituents is generally raised as the increased ingestion of water flushes salts and metabolites from the tissues. There is no simple relation, however, between the increase of the different constituents, for instance N and Cl (Heilner, 1906).

Administration of large quantities of water causes a considerable *temporary increase in the urinary nitrogen*, as much as 34 per cent (Neumann, 1899). The excess is excreted mainly as urea, the uric acid being often unchanged. Fairhall and Hawk, 1912, found the *uric acid output* in man decreased, while the allantoin was increased. The excretion of the *phosphates and sulfates* is also increased. The removal of *chlorides* is so extensive that their percentage in the urine soon falls to a low figure. Wilson and Hawk, 1914, reported that the ingestion of additional water, moderate or abundant, causes a temporary decrease in the daily output of *chloride*, presumably through the need of equalizing the osmotic pressure of the retained water. The *ammonium* is increased (presumably as a consequence of the heightened gastric acidity), the *phosphate* unchanged, the *acidity* variable.

Increased Metabolism.—The excessive excretion of metabolites is mainly due to the "*flushing out*" of the tissues by the diuresis (Haas, 1908). If this were the only cause, the continued excessive administration of water would soon exhaust the stored waste products, and their excretion would fall rather below the normal figure. Actual results show that this holds for the chlorides, but not for N, P or S; their excretion remains permanently increased, although it does not remain at the original high figure (Edsall, 1900). There must therefore be *increased production of these metabolites.*

Conditions that Modify Urinary Water Excretion.—The degree of diuretic response to water ingestion is modified by the needs of the body and by the competence of the kidneys. Disturbances of urinary water excretion are among the most conspicuous functional manifestations of *nephritis* (Peters, 1932). The *tissue needs* for water are not necessarily reflected in the blood; *i.e.*, the diuretic response is not definitely related to the hemoglobin concentration (Haldane and Priestley, 1916). *Isotonic solution* of sodium chloride or bicarbonate, taken by mouth, produces diuresis much more slowly than equal quantities of water, in twenty-four to forty-eight hours, instead of two to three hours (Adolph), probably owing to slower absorption.

Temperature regulation is one of the principal factors of water diuresis. Warm environment reduces diuresis more than corresponds to the extrarenal loss of water, or to diminished absorption (Heller and Smirk, 1932). In fever, water is retained during the rise of temperature, and mobilized in defervescence. Binding down a rabbit alters its temperature regulation and therefore its diuresis. This is related to the *sugar level of the blood* (Barbour). Hyperglycemia, as by the ingestion of sugar, produces hydremia and diuresis; *insulin* hypoglycemia results in blood concentration (H. Marx, 1937). *Muscular exertion* diminishes diuresis, partly by leading to water loss by evaporation. Violent exercise, entailing accumulation of lactic acid and large oxygen debt, may suppress renal water excretion for an hour, presumably by the rise of osmotic concentration in the muscles (Hellebrandt, Walters and Miller, 1936). *Hemorrhage* leads to marked water retention, and water administration is as effective for restoring the blood volume as saline injection, though not so rapid. *Laparotomy,* even under local anesthesia and without handling of the intestines, reduces water diuresis by 90 per cent, in rabbits, because of retardation of intestinal water absorption (Heller and Smirk, 1933).

Parenteral administration of water, as such, produces little or no diuresis. For intravenous injections, this could be explained by the osmotic swelling of the renal epithelium, owing to hypotonicity of the blood, leading to compression of the blood vessels. Laking of the blood corpuscles would also diminish urine flow. Grindsberg, 1912, and Cow, 1914, however, suggested that the presence of water in the intestinal canal leads to the production and absorption of a diuretic substance. This has found experimental support in the extraction of potent diuretic substance from small intestines (Schmid, 1938).

General Effects of Water by Intravenous Injection.—The immediate effects of small amounts, slowly introduced (and especially of *hypodermic injections*), resemble those following the injection of isotonic salt solutions. The changes in metabolism and urine constituents are probably similar to those which occur on taking water by mouth. Larger doses and rapid injection introduce important modifications. Hemoglobin appears in the urine, from the laking of the blood corpuscles. The respiration is slowed and the blood pressure is lowered. The central nervous system shows rather late paralysis and convulsions. The excretion of water occurs mainly by other channels, so that there is usually a serous diarrhea, increased salivation, and so forth. The fatal dose of water (by intravenous injection) is somewhat smaller than that of normal saline solutions; distilled water is again somewhat more toxic than well water.

The *therapeutic uses of water diuresis* are chiefly to dilute the urine, to diminish its irritation and to flush out bacteria in *inflammations of the urinary passages*, in acute and chronic cystitis and in prostatic obstruction. The dilution is also useful to check the formation of urinary calculi of all kinds. The increased flow serves *to flush out tubular detritus* in nephritic oliguria; but the limited capacity of water excretion by such patients must not be exceeded. The increased N elimination following liberal water administration lowers the abnormally high N figures of the nephritic blood.

A certain minimum amount of water must be excreted by the kidneys *to carry the normal metabolites in solution.*

The quantity depends on the concentrating ability of the kidneys, which is reflected in the maximal specific gravity. To excrete the daily normal of 35 Gm. of waste products requires 473 cc. of urine, of sp. gr. 1.029 to 1.032; but 1439 cc. at 1.010 to 1.014. Less water leads to nitrogen retention (Lashmet and Newburgh, 1932). An output of 1500 cc. suffices for all ranges of function; larger quantities are needed only for flushing the urinary passages in infection (Maddock and Coller, 1937).

The *removal of poisons by diuresis* is not very successful, for poisons are generally nonthreshold substances, and their elimination is therefore not increased by hastening the passage through the tubules, but only by increased glomerular filtration. Water diuresis acts chiefly to lower the concentration of the excreted poisons. Energetic diuresis, by water or by intravenous saline or glucose, can save animals from *slightly* superfatal doses of strychnine (Eggleston and Hatcher, 1917; Kleiner and Meltzer, 1917), but is quite inefficient against diphtheria toxin (Sansum, 1918).

Retention of water does not occur under normal conditions, as the water-excreting capacity of normal kidneys is fully equal to the capacity of water absorption from the alimentary tract—as may be imagined when it is remembered that over 100 liters of fluid normally filter through the glomeruli. Water retention therefore occurs only when the renal functions are seriously upset by nephritis, by cardiovascular disease or by pitressin. All tissues participate in temporary storage of water. In cardiovascular disease, the excess fluid is chiefly in the lymph spaces; with nephritis and pitressin it is also intracellular.

The *water content of muscle* (and similarly of liver), as determined by biopsy, is increased by isotonic infusions, pitressin injection, starvation, morphine withdrawal. It is decreased by hypertonic saline infusion and by caffeine. It is not altered by anesthetics or by epinephrine (review, Adolph).

The *pituitary control* of water elimination is discussed under that subject (see Index). It is responsible for the antidiuretic effect of certain sensory reflexes (Verney; Haterius, 1939), and probably also for the effect of water deprivation and of temperature. The loss of water by frogs in dry environment is inhibited by the injection of pitressin and of pitocin (Boyd and Whyte, 1938).

Hydremia.—The drinking of a large quantity of water produces slight hydremia, shown by slight decrease in the electric conductivity of the serum (T. M. Wilson, 1905). Haldane and Priestley, 1916, attributed this to the passage of salts into the intestines. Blix, 1916, found that the administration of water to well fed rabbits could increase the water content of their body by a maximum of 11 per cent. Fasting and withholding water diminished it, also by a maximum of 11 per cent on the second day. After that it remained constant. Mercuric chloride nephritis also produced hydremia.

Blood Pressure.—Increased ingestion of water (for man, 3 liters beyond the normal) is said to produce a material lowering of the systolic and diastolic pressure, normally and in hypertension (J. B. Orr and Innes, 1922).

"Water Intoxication."—Excessive retention of water produced experimentally by intensive forcing of water (administering 500 cc. every hour to a dog by stomach tube) reduces the hemoglobin by about 15 per cent, the serum protein by somewhat more, and serum chloride by about 30 per cent (C. H. Greene and Rowntree, 1924). If posterior pituitary solution is injected at the same time, still greater retention is obtained, and the animals develop serious and fatal symptoms. They are not due to increased volume of extracellular body fluid, but to reduction of its osmotic concentration, and consequent increase of intracellular fluid, particularly cerebral edema (review, J. P. Peters, 1944). The phenomena begin with restlessness, asthenia, diarrhea, salivation, nausea, retching and vomiting. Motor symptoms develop tremors, twitching and ataxy, progressing to attacks of extremely violent tonic and clonic convulsions, alternating with collapse. Electroencephalogram changes in rats are described by E. Gellhorn and Ballin, 1946. The intracranial pressure is increased and the temperature falls. The animal passes into stupor and coma, and dies in four to twelve hours, or after several days. The only characteristic lesion found at necropsy is cerebral edema. Pressure symptoms may be relieved by intravenous injection of hypertonic saline solution (Rowntree, 1926).

The threshold for electric shock and metrazol convulsions is lowered by cellular hydration, raised by excessive administration of water or by depletion of extracellular electrolytes, or additively by both. Anti-epileptic drugs raise the convulsive threshold more effectively in animals in which cellular hydration is high (E. A. Swinyard *et al.*, 1946).

Dehydration, a deficit of tissue water, causes collapse and shock. It may be produced through excessive loss of fluid, or when water is withheld, or not absorbed, as in diarrhea. It occurs frequently in surgical patients. Loss of 10 per cent of the body water is totally disabling to men (review, J. P. Peters, 1944).

Men walking in the hot desert without drinking water become exhausted when the water loss reaches 4 to 8 per cent of the body weight; with external temperature of 105° F. this occurs in four to seven hours. Thirst sensation is usually only moderately unpleasant. Drinking water freely prevents the exhaustion, and it is greatly relieved in fifteen minutes by drinking as much as desired. The blood volume is markedly diminished (E. Adolph *et al.*, 1944). In normal subjects dehydrated by withholding fluids, febrile phenomena appear when the loss of water reaches about 6 per cent of the body weight (3600 cc. for a 60 Kg. individual), coincident with the reduction of the urine output to a degree insufficient to remove the normal waste materials, so that the nonprotein nitrogen of the serum rises above 40 mg. per 100 cc. When water is again given, almost the whole of the intake is retained until the tissue fluid deficit (*i. e.*, about 3600 cc.) has been made good (Maddock and Coller, 1937). *Renal clearances* indicate that dehydration does not affect glomerular filtration, but solely tubular reabsorption (D. A. K. Black *et al.*, 1942), probably by release of posterior pituitary antidiuretic hormone, through a central, not through a peripheral mechanism (review, M. Pickford, 1945). The *sodium and chloride* of the urine become minimal as dehydration advances, and their concentration in the plasma rises (J. R. Elkinton and Taffel, 1942). The destruction of protein is increased during the withdrawal, and when water is resumed the stored metabolites are washed out, leading to a greatly increased excretion (Landauer, 1895; Straub, 1899; Spiegler, 1901).

Thirst is a delicate reaction, attuned both to the volume of fluid in the body and to the concentration of solutes (A. Gilman, 1937). It does not originate in dryness of the oral mucosa, for it is not affected by cutting the oral nerves (R. T. Bellows and van Wagenen, 1939), and it can be slaked by giving water by stomach tube (C. Fisher *et al.*, 1938).

A *dehydration therapy of epilepsy* was proposed by McQuarrie, 1929, who conceived epilepsy as caused by hydration pressure. Other observers, however, have failed to find that the seizures are either benefited by water limitation, or increased by overconsumption, acute or prolonged (Wilson and Limberger, 1933).

Treatment of Dehydration.—If fluid can be absorbed from the intestines, as in hemorrhage and often in traumatic shock, oral or rectal administration of water appears to maintain the blood volume better than the intravenous injection of saline or even of acacia solution, although it does not act so promptly (O. H. Robertson and Bock, 1919).

Intravenous injection of dextrose is preferable for parenteral administration in surgical dehydration, as it has a food value, prevents ketosis and protects the liver. Sodium chloride disposes to excessive salt retention, but should be used if there has also been excessive loss of salt, through vomiting or sweating (Maddock and Coller, 1937).

Alleviation of Water Deprivation.—Sea water contains almost twice as much salt as the most concentrated urine, and is therefore so greatly hypertonic that it actually increases dehydration and hastens death if consumed undiluted by mouth or by enema (R. F. Bradish *et al.*, 1942). The problem must therefore be met by restricting the need for water (avoidance of heat and exertion), stretching the available supply by dilution with sea water, and by methods of desalting.

The minimum daily requirement of water, under working conditions and with enough carbohydrates to prevent ketosis, is 825 to 1000 cc. Under stress, the daily allowance may be reduced to a pint. Sea water may be added to this in the ratio of not more than 1:4 or 5, not to exceed 200 cc. per day, equivalent to 6 Gm. of salt (A. C. Ivy, 1944). The most practical method of desalting is by adsorbents. A silver and urate method is described by C. R. Seagrave, 1944.

Rats, unlike man and dog, are able to concentrate their urine somewhat above sea water, and therefore survive slightly longer when drinking sea water than with complete water deprivation (E. F. Adolph, 1943).

Local Actions.—Water is mildly stimulant and irritant to sensitive surfaces.

The growth of artificial cultures of frog's tissues is hastened by diluting the serum of the culture fluid (Ruth, 1911).

The effects of baths and similar hydrotherapeutic measures depend upon reflexes due to the physical action of temperature and so forth.

Digestion and Absorption of Food.—Ingestion of water with meals has decidedly beneficial effects upon all the digestive organs, even when the quantity of water is large (1 liter with each meal), provided that the food is thoroughly masticated. It aids the digestive action of the saliva, increases the flow of gastric juice, its pepsin and acidity, and thus presumably the flow of pancreatic juice. It secures better absorption of the food, leaving less material for the intestinal bacteria, decreasing their number and the putrefactive processes. The same beneficial effects are secured with distilled water, which has no detrimental effects even in prolonged fasting experiments (Hawk, 1914). These actions are utilized in the treatment of dyspepsias. Water is often useful in nausea. It is also valuable as a diluent for irritant drugs. Excessive water consumption would probably be harmful in gastric atony.

Up to 1 liter of water has no effect on the gastric emptying time of the farina-barium test meal in normal men (E. J. Van Liere and Northup, 1944). The secretion of *acid gastric juice* is increased (Heidenhaim, 1879; Pavlov; Foster and Lambert, 1908). Even 50 cc. strongly increases the acidity and peptic activity (Bergheim, Rehfuss and Hawk, 1914). The gastric stimulation does not occur in all cases. It is perhaps due to the washing of the hormone gastric into the intestine (Ivy, 1918). The flow of *pancreatic juice and bile* is also stimulated. The dilution would accelerate the action of the digestive *enzymes*. The diastatic efficiency of saliva is increased, the optimum being reached with 1:7 dilution (Bergheim and Hawk, 1913). The *discharge of the gastric contents* is hastened (at least after a meal of meat, although not with potatoes; Hedbom and Cannon, 1909). The water does not actually mix with the gastric contents, but passes along a trough formed on the surface (Cohnheim). The *rate of discharge* of water from the fasting human stomach varies normally between 100 and 400 cc. per minute. Older figures were higher, but misleading (Ivy, 1918). *Hunger contractions* are allayed by drinking water (Carlson, 1913). The utilization of fats and carbohydrates is not affected (Blatherwick and Hawk, 1914).

Distilled water is more injurious than ordinary water to aquatic animals and to excised tissues, partly because of the total absence of salts (especially of calcium, thus probably altering the permeability of the plasma membrane; R. H. True, 1914), and partly because it often contains traces of copper and ammonium compounds. *This toxic action can not occur by the drinking of distilled water by higher animals,* which obtain their salts from food; nor is distilled water detrimental in nephritis (Marcus, 1907).

The U.S.P. describes *Distilled Water, Sterilized Distilled Water* (which must not be used for parenteral administration) and ***Water for Injection,** "distilled, sterilized and stored in sealed or other suitable containers, so that it is free and remains free from pyrogens." It is tested for this on rabbits. The *pyrogenic effects* observed with intravenous injections of solutions prepared from ordinary distilled water are due to substances formed by bacterial contamination, which is transmitted by flasks and tubing. The pyrogenic substance is destroyed by boiling for six hours, or autoclaving from three to four hours; but the ordinary time of sterilization tends to increase its activity (F. Seibert, 1923, 1924; review, C. M. Nelson, 1939).

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MINERAL WATERS

The action of natural mineral waters has been known empirically since remote times. Their use came about probably by accidental observation and also through the marked taste which they possess.

Spring and Artificial Mineral Waters.—A striking observation was early made that these mineral waters, when used at their source, appear to be more effective than artificial compounds of practically the same composition, or even than the same water when used at a distance. Diverse explanations for this were advanced, such as "tellurial" forces, some mysterious property imparted to them by the earth. Some mineral waters are slightly radioactive. Others stress minimal traces of rare elements. Still others professed that the artificial waters—even if they contain the same elements in the same proportions—do not contain them in the same state of combination. In fact, however, mineral waters are simply solutions of the ingredients of the soil, and have only the action of those ingredients present in notable amount. The difference between the waters taken at the natural source and the artificial solutions is due to the accessory conditions, chiefly *hygiene and climate;* the rest, the freedom from care and business pursuits, the exhilarating effect of improved hygienic, atmospheric and scenic conditions, better regulation of all the habits, of diet, exercise, and so forth. The mere drinking of large quantities of fluid is also something which it is difficult to enforce at home, but which the patient does regularly in watering places. The effect of mineral *baths* is purely local and reflex. There is practically *no absorption* of the dissolved salts through the skin. The effects are in general the same as with hydrotherapy, except that they are somewhat stronger.

Mineral waters are usually *classified* according to the contained salts into: 1. Plain saline (NaCl). 2. Carbonated: (*a*) plain; (*b*) alkaline ($NaHCO_3$); (*c*) saline (Na_2SO_4). 3. Magnesia. 4. Sulfur. 5. Chalybeate. Many mineral waters belong partly to several classes. Occasional constituents of small importance are Ca, I, Br, Li and As.

DEUTERIUM OXIDE (HEAVY WATER)

Water formed from the heavier isotope of hydrogen, D_2O, does not appear to be directly toxic, but to become so by displacing ordinary water, the place of which it cannot quite take because it greatly reduces the rate of all physico-chemical processes (H. S. Taylor, 1934).

Living cells cannot distinguish between the isotopes of the same element, and treat them practically alike. This is utilized for "*tagging*" atoms to learn their fate in the body (review, R. Schoenheimer and Rittenberg, 1940).

Hydrogen occurs as three isotopes, protium, deuterium and tritium, with the atomic weights of 1, 2 and 3 (E. J. Crane, 1934). Protium is by far the most abundant, but is mixed with small amounts of the others. Deuterium constitutes 0.02 per cent of all hydrogen and its combinations in nature, including all water, free and bound, and all organic hydrogen compounds. The viscosity of deuterium oxide is 23 per cent greater than that of ordinary distilled water.

Toxicity.—White mice die in about a week if they drink heavy water exclusively, or if it is administered at the rate of 1 cc. per 10 Gm. per day, orally or hypodermically, 40 to 50 per cent of the body water being replaced by deuterium oxide by this time.

Course.—The symptoms begin on the first day, with pilomotor stimulation; then follow anorexia and weight loss. The temperature and metabolic rate begin to decline about the fourth or fifth day, and the latter falls to about a third of the normal on the day before death. Marked jumping reflexes appear on the fifth day, then ataxia, and toward the end, cyanosis and dyspnea. The same phenomena develop, but more slowly, if half of the drinking water is replaced by deuterium oxide (Barbour and Tracy, 1936).

Sympatheticomimetic Actions.—Replacement of a fifth of the body water by deuterium oxide is not fatal to mice, but causes symptoms of sympathetic stimulation, erection of the hairs, exophthalmos, increase of basal metabolism by 20 per cent, usually rise of temperature. These are abolished by ergotoxine. These effects increase with replacement of half of the body water (Barbour, 1937; Barbour and Herrmann, 1938). The melanophores of the isolated scales of the fish Fundulus are contracted as with epinephrine, and this is prevented by ergotoxine (Barbour and Bogdanovitch, 1937). Barbour suggests that deuterium oxide protects epinephrine from decomposition.

Excised hearts of frogs and turtles are slowed by immersion in Ringer's solution made with 20 to 96 per cent deuterium oxide (Barnes and Warren, 1935, 1937).

Cataleptic contractions are produced by the direct application of deuterium oxide to the cerebral cortex of rats, cats and monkeys, or by meningeal injection into the parietal region, provided that the local concentration reaches about 20 per cent (J. B. Herrmann and Barbour, 1937). Encephalograms indicate depression. No effects result from application to the spinal centers of cats and frogs, or to nerves or skeletal muscles of frogs (Herrmann, 1939).

Water Loss and Hyperthermia.—When 40 per cent or more of the water consumed by mice is replaced by deuterium oxide, the insensible water loss is decreased, relative to the CO_2 output. The effect is prevented by ergotoxine. When a third of the body water has been replaced, metabolism is also increased, resulting in hyperthermia (Barbour and Rice, 1938).

Metabolism.—Continued oral administration of 40 per cent D_2O to mice at the rate of 1 cc. per Gm. of body weight per day, leads to increased metabolic rate, beginning on the fifth to tenth day. This effect is not produced by more dilute (30 per cent) or more concentrated (50 per cent) solutions. With hypodermic injection of 4 cc. of 99 per cent D_2O, the metabolic rate is reduced by more than 50 per cent, within forty-eight hours; without other symptoms, except temporary respiratory depression (Barbour and Rice, 1938).

The *normal growth rate of young mice* is decreased by replacing 8 to 9 per cent of their body water with D_2O for two weeks. No pathological lesions were found. Smaller doses, replacing more slowly to 8 per cent, did not interfere with development to maturity and reproduction, but the litters were small and their mortality was high (Hansen and Wülfert, 1938).

Tumor growth in mice is retarded at least 50 per cent when 20 per cent of their water content has been replaced by D_2O, by keeping the animals on 40 per cent D_2O. Normal mice survive this for at least four months, but the treated tumor mice die earlier (Barbour and Allen, 1938).

The *segmentation of frog eggs* is retarded by D_2O, above 5 per cent (Ussing, 1935). *Yeast fermentation* and *catalase action* are also retarded (H. S. Taylor, 1934).

Osmotic Effects.—Because of its lower vapor pressure, D_2O is hypertonic to corresponding solutions in H_2O. This may explain the thirst it causes and the burning sensation on mucous membranes (S. C. Brooks, 1937). *Hemolysis* of mammalian erythrocytes requires about twice as long as with ordinary water. This is probably explained by the higher viscosity and lower motility of D_2O (Parpart, 1935).

Deutero-alcohol, C_2O_5OD, is 1.1 to 1.6 times more narcotic than C_2H_5OH for fish and larvae (Hansen and Dybing, 1938).

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CATHARTIC SALTS

A number of soluble salts are not absorbed readily from the alimentary canal and do not produce marked direct systemic actions, unless they are injected into the circulation. When they are given by the mouth, their direct action is confined to the intestine, producing catharsis with soft or fluid, painless stools. The salts of magnesium, and the sulfates, phosphates, tartrates and citrates of sodium or potassium are chiefly used as saline cathartics. The cathartic action is mainly the result of the retention of fluid in the intestine by the osmotic action of the unabsorbed salt, for this must retain sufficient fluid to preserve itself isotonic with the blood (Wallace and Cushny, 1898). The distention by this fluid provokes the intestines to contraction, and the contents are thus rapidly propelled (Trendelenburg, 1917). The passage through the intestines is therefore hastened, although the salts as such do not directly increase peristalsis (Legros, 1869; Hay, 1883; Padtberg, 1909). The contraction waves so set up may travel rapidly over the intestines, and secure evacuation before the cathartic salt itself has reached the rectum

(Herz *et al.*, 1908). Hypotonic solutions also cause direct stimulation of the muscles; hypertonic solutions produce short stimulation followed by depression; but the stimulation may expel the solution before the depression sets in (Baur, 1925; v. Oettingen and Sollmann, 1926). In any event, the solutions would soon become isotonic. Magnesium is directly depressant to the intestinal muscles, and is utilized against the spastic contractions of barium and of lead colic. Ordinarily this depression is more than offset by the distensive stimulus; but it may be important for overcoming intestinal spasm (Sollmann and Rademaekers, 1925).

The *popular synonyms* of the cathartic salts testify to their extensive use. Those that occur in natural mineral waters were named after the springs, such as "*Epsom salts*" (magnesium sulfate), "*Carlsbad salts*" (sodium sulfate and bicarbonate). "*Glauber's salt*" (sodium sulfate) was named for a German chemist and physician of the seventeenth century; "*Seidlitz powders*" (effervescing sodium and potassium tartrate) for a Bohemian carbonated spring; "*Rochelle salts*" (sodium and potassium tartrate) for the French city where this salt was made from the "tartar" of wine casks; "*Cream of tartar*" (acid potassium tartrate) and "*Salts of tartar*" (potassium carbonate, obtained originally by the calcination of the preceding) are derived from this source.

Two types of cathartic response may occur, as has been indicated: the *early*, within an hour, due to the "duodeno-colonic reflex" (probably not a reflex, but the propagation of a distention and contraction wave); and the *delayed*, in three to twenty-four hours, due to the retention of fluid in the intestine by the osmotic pressure of the unabsorbed salt.

The *early type* is illustrated by the observations of Herz *et al.*, 1908, in man, that drachm doses of epsom salt may cause watery evacuations within an hour of greater volume than could be explained by osmosis. The stools of the following morning, which contain distinctly more of the salt, had a normal solid consistency. The salt itself may travel rapidly through the intestines; for instance, 5.7 Gm. of magnesium sulfate were recovered from a stool that was passed three hours after the administration of 10 Gm. of magnesium sulfate in 400 cc. of water (Ury).

Roentgenoscopic observations of A. Bergmann, 1929, on man show that before the magnesium sulfate has left the stomach, it hastens the passage of the contents of the large intestines, from the cecum and through the colon, from the normal time of three to six hours to less than half an hour. The passage through the small intestines was shortened to forty to sixty minutes (by distensive stimulation), when the salt reached the intestines. This coincides with the early x-ray studies of Padtberg, 1909, that the emptying of the stomach is delayed, but that the passage through the intestines is quickened. Colon antiperistalsis is not inhibited; but it does not lead to the concentration of the contents, because of the osmotic retention. The fecal matters are therefore more fluid, and this hastens their expulsion. The saline catharsis is not checked by morphine, unless this is timed so as to secure gastric retention of the salts.

With *permanent fistulas* in dogs, G. B. Roth and Crittenden, 1934, observed no effect on gastric or intestinal motility when isotonic solutions of sodium or magnesium sulfate were confined to the stomach; hypertonic solutions decreased gastric and increased intestinal motility. When introduced directly into the intestines, hypertonic as well as isotonic solutions increased intestinal motility. When solutions at body temperature are infused through Thiry-Vella *jejunal loops* of trained unanesthetized dogs, isotonic sodium sulfate and magnesium sulfate produce moderate stimulation of motility, followed by depression of motility and tonus if the magnesium infusion is prolonged. Hypertonic sodium chloride or of sodium or magnesium sulfate depresses the motility, with brief periods of spasticity (E. W. Ligon, 1943).

Osmotic Factor in Cathartic Action.—Buchheim, 1854, claimed that the increased water in saline catharsis comes from the alimentary canal and not from the blood. Colin, 1854, showed that concentrated solutions of cathartic salts increase in volume when placed in an intestinal loop. Wallace and Cushny, 1898, demonstrated conclusively that saline solutions placed in the intestines become and remain isotonic with the blood, and that therefore the amount of fluid held in the intestines depends on the amount of salt which remains unabsorbed.

Difficultly Absorbable Ions.—The most important cathartic ions are: of the cations, Mg; of the inorganic anions, SO_4 and PO_4; of the organic, tartrates, citrates, fumarates, lactates and malates. Certain sugars, particularly milk-sugar and mannite, also act as osmotic cathartics. Many other solutes that are difficultly absorbable are not available as cathartics; *f. i.*, Ca and Sr are largely converted into insoluble carbonates, and so become osmotically inactive; oxalates and fluorides are toxic; the metallic ions precipitate proteins and act as astringents.

Easily Absorbable Ions.—Of the *cations*, ammonium is the most readily absorbed; then come the alkali metals. The earthy metals are not easily absorbable. Of the *anions*, the chlorides, bromides, iodides, nitrates and acetates are rapidly absorbed. The *cause of the different absorbability* has not been satisfactorily explained. There are striking analogies between the absorption of ions by the intestine and by muscle, and the solubility of their soaps and calcium salts, but it is not yet clear whether this is a coincidence or has a deeper meaning.

Conditions that Influence Absorption.—The cathartic salts are not completely unabsorbable. The ratio of unabsorbed to absorbed varies with conditions, but generally the amount in the feces and urines is about equal for sodium sulfate; the feces contain relatively more magnesium. The degree of absorption depends primarily on the time of sojourn in the intestines, so that the urinary excretion and its accompanying diuresis are reciprocal to the catharsis. Absorption of the salt and diuresis are favored (and catharsis therefore decreased) by dryness of the tissues, restriction of fluid income, and concentration of the solution (Matthew Hay, 1883). Conversely, *dilution favors catharsis.* Cathartic salts should therefore be administered as dilute or isotonic solutions, if the object is merely the evacuation of the intestines. Hypertonic solutions are indicated for the removal of fluid, especially edemas, as they utilize diuresis as well as catharsis.

Fate of the Cathartic Salts.—The portion which is not absorbed is eliminated promptly by the *feces.* The other salts of the feces are also markedly increased; the organic matter only slightly (Hay). The sulfates are in part reduced in the colon to sulfides, which give their characteristic odor to the feces (R. Kochmann, 1920). *After absorption,* the cathartic ions are eliminated largely by the urine, producing a diuretic action. With sodium sulfate, one-third to one-half of the excreted salt is in the urine. A considerable portion of the sulfate of magnesium may be retained in the tissues, the excretion extending over several weeks (Mendel and Benedict, 1909). The urinary excretion of the sulfate ion follows a characteristic curve, independent of the water excretion (Möller, 1927).

Absorption of other substances is in general delayed and diminished by saline catharsis. This may be of some importance in the treatment of poisoning (Macht and Finesilver, 1922).

Diuretic Action.—All the cathartic anions are readily excreted by the urine, and therefore act as saline diuretics, rather more effectively than equivalent amounts of sodium chloride. Because of the abstraction of water by the feces, the urine flow is generally decreased in the first twelve hours; it is then increased for about a day (Hay). The diuretic effect is proportional to the quantity of the salt absorbed, and therefore inverse to the catharsis. It is greatly increased by the oral administration of theophylline (Möller, 1927). Sodium sulfate diuresis increases the gas consumption of the kidney (Bainbridge and Evans, 1914).

Reaction of Urine.—$MgSO_4$ markedly increases the ammonium and acidity of the urine; Na_2SO_4 and MgO decrease the acidity, with subsequent return to the normal reaction (de Jager, 1911).

Concentration of the Blood.—Hay found that this is increased shortly after the administration of concentrated, but not of dilute, solutions of cathartic salts. The blood count rises from 5,000,000 to 7,000,000 by the abstraction or retention of fluid in the intestines. It returns to normal within four hours, even if no fluid has been taken, since the saline solution is gradually absorbed from the intestines. When diuresis sets in, the blood count again rises to 6,000,000, even if the salt has been taken diluted.

Metabolism is not measurably increased by the increased peristalsis of saline cathartics (Benedict, 1914).

Temperature.—Saline cathartics were used in fevers, for their supposed "cooling" effect. Hay found no reduction of the internal temperature.

Other Theories of Saline Catharsis.—A number of other factors have been suggested, such as inflammatory irritation, stimulation of intestinal secretion, and muscular stimulation by osmosis, ion action, or the withdrawal of calcium. None of these rests on adequate evidence, and they probably play at most a minor part.

M. Hay, 1883, believed that the salts excite a secretion of fluid into the intestines, which is partly balanced by absorption. His experimental results are explainable more simply on the basis of osmosis. Headland, 1867, believed that the salts are first absorbed, but reexcreted into the intestines, and that they stimulate secretion during their elimination; but Thiry, 1864, found no secretion in his fistula. The theory of Carl Schmidt, 1850, that the fluid is a transudate is without foundation. Chiari, 1910, suggested that the precipitant effect of most of the cathartic ions for calcium could increase the excitability of the intestine. This is only hypothetical.

Parenteral Administration.—Catharsis was reported from intravenous, hypodermic or intramuscular injection of sodium or magnesium sulfate by Bernard, 1857, and by J. B. MacCallum, 1903 and 1906. Most observers, however, have failed to obtain increase of peristalsis and catharsis when proper precautions were taken to exclude exposure and asphyxia (Auer, 1906, 1908; Mendel and Benedict, 1909). Joseph and Meltzer, 1910, and Sollmann and Rademaekers, 1925, found, with a careful technic, that intravenous or intramuscular injection of magnesium inhibits peristalsis. *Hypodermic injection* is also without result, except when made under the abdominal skin. The success in this case is reflex, for injections of NaCl or $ZnSO_4$ in this region are also cathartic (Hay).

Excised Intestines.—The phenomena are described under the respective ions.

Therapeutic Uses.—The cathartic salts are used to empty the intestines in constipation and the like, and to dry the tissues in edemas.

They are useful and effective as simple cathartics, especially in digestive disturbances, in hyperchlorhydria, with alkalis, as magnesium hydroxide or Carlsbad salt; and against occasional constipation in alternation with emodin or demulcent laxatives. They do not meet the motor deficiency of chronic constipation so efficiently as the cascara group; they are often rather unpleasant to the patient; they may lose in efficiency on continued use, their prolonged employment accustoms to an abnormal type of peristalsis (Bastedo, 1914), and they are not very effective in obstinate constipation. As hydragogue cathartic for the removal of edemas, the absence of irritation renders them generally superior to the drastic vegetable cathartics; their diuretic effect is a further aid.

Administration as Laxatives.—For this purpose, the salts should be given in dilute solution, a teaspoonful to tumbler, since they are less distasteful and act more promptly (one to four hours). The laxative dose of the usual salts is 5 to 10 Gm. (1 to 2 drachms). They are best administered before breakfast, to hasten their passage through the stomach. If this is delayed, as with bedridden patients, they are less efficient and somewhat irritant. Some exercise is useful after taking salts.

Administration in Dropsy.—Large doses (15 to 30 Gm., $\frac{1}{2}$ to 1 ounce) should be given in concentrated solution ($\frac{1}{2}$ tumbler), also before breakfast. The concentrated solutions act more slowly than the dilute mainly because they tend to close the pyloric sphincter; but they remove more fluid since they also increase diuresis. They are used especially in cardiac edemas. Retention and accumulation of the salt may occur in nephritis, and magnesium salts may become dangerous. Concentrated solutions are also employed to reduce the secretion of milk.

Source of the Fluid in the Stools.—If the cathartic salt is administered in hypertonic solution, it withdraws some fluid from the tissues (unless water is swallowed at practically the same time), but the amount of fluid needed for this is insignificant. Ordinarily, however, the quickened peristalsis interferes with the reabsorption of other fluids present in the intestines, and this may increase the fluid of the feces by considerably more than the amount held by the unabsorbed salt. Three to 10 liters of fluid are daily excreted into the digestive tract of man, and 1 or 2 liters more are introduced with the drink and food. As the normal daily feces contain only about 100 cc. of water, the daily absorption of liquid from the intestines is over 4 liters; *i. e.*, considerably more than is needed to furnish all the liquid of severe saline catharsis. The latter, therefore, does not directly abstract water from the tissues or effusions, but tends to dry them in the same manner as if the water income were restricted by any other means.

The *choice between the cathartic salts* is largely determined by their *taste*. The sodium sulfate has, perhaps, the most disagreeable taste; the magnesium sulfate somewhat less so. Sodium phosphate and Rochelle salt are materially less disagreeable and act promptly, usually within an hour after breakfast. MgO and $MgCO_3$ act as alkalis as well as cathartics. Acid sodium phosphate renders the urine acid. The best corrective for the *taste* of the salts is ample dilution with water, when this is permissible. Some of the salts are official in *effervescent form; i. e.*, mixed with sodium bicarbonate and citric or tartaric acid.

SODIUM SULFATE

This is a typical cathartic salt, almost free from ion action. On account of its disagreeable taste it is not much used, except in veterinary practice, but it forms an important ingredient of many mineral waters, *e. g.*, Carlsbad. The kidneys are more permeable to sulfate than to chloride ions, so that its intravenous injection produces a copious diuresis. The secretion of gastric juice is not increased.

The *stimulant actions of hypodermic or intravenous injections* of sodium sulfate on the circulation and respiration appear to surpass those of sodium chloride. An isotonic solution (2 per cent of the dried or 4 per cent of the crystalline salt) is used in quantities of 500 to 1000 cc. The addition of sodium sulfate, 1:1000 of blood, perfused through the vessels of *excised* intestines stimulates peristalsis and is antagonistic to magnesium depression (Glénard, 1913).

Sodium Sulfate, U.S.P. (*Glauber's Salt*); $Na_2SO_4.10H_2O$. Large or granular colorless crystals, of bitter saline taste. Freely sol. in water (1:1.5); practically insol. in alc. All sulfates are *incompatible* with calcium and lead. Dose, 2 to 15 Gm., $\frac{1}{2}$ to 4 drachms, diluted.

Sodium persulfate, $Na_2S_2O_8$, is fifty times more toxic than the sulfate, for rabbits, on intravenous injection. It destroys the red blood corpuscles and produces severe changes in the kidneys, lungs and liver (Da Val, 1933).

TARTRATES

These are difficultly absorbable, and are therefore saline cathartics having the advantage of a relatively unobjectionable taste. The potassium-sodium tartrate or Rochelle salt is commonly used. Acid potassium tartrate (cream of tartar) acts as a mild acid; being relatively insoluble, the acid action extends into the intestines and here stimulates peristalsis. It is therefore more actively cathartic. Cream of tartar and tartaric acid effervesce with sodium bicarbonate, and are used in baking powders (see Index), effervescent drinks, and so forth. The tartrates are not readily burned in the body, and therefore do not act as alkalis and diuretics so strongly as do most other organic anions. When introduced into the circulation, they have a rather high toxicity by immobilizing calcium and by injuring the renal epithelium; but this need not be feared from therapeutic doses (Post, 1914). The toxicity is probably also lower for man, as the tartrates are more readily destroyed.

Fate.—But little tartrate is destroyed after absorption. Dogs, rabbits and rats excrete it promptly and completely by the urine, both after oral and parenteral administration. This would probably also hold with man for parenteral administration; but with oral administration, less than 20 per cent appears in the urine, and none in the feces, even after purgative doses. The remaining 80 per cent is probably destroyed by bacterial action in the large intestine. Guinea pigs behave as man in this respect (Underhill *et al.*, 1911). Although tartrates are not oxidized, the administration is said to render the urine alkaline (Pratt and Swartout, 1933).

Toxic Actions of Tartrates.—The effects on calcium are similar to those described under citrates. Small doses produce only the renal injury; larger doses, also muscular and nervous symptoms. The cardiac excursions are decreased, especially in systole, with moderate slowing. The blood pressure is unchanged, the kidney volume slightly increased. The effects may be acute or subacute, according to dose (Salant and Smith, 1914). The four stereochemic isomers behave somewhat differently toward calcium and therefore have a different toxicity (Chio, 1912). Salant and Smith, 1913, found that the d. and l. had the same toxicity for frogs and rabbits; but the resistance of different animals varies greatly.

Excised Intestine and Isolated Frog Heart.—The effects of the various tartrates, succinates and malates, on the small and large intestines are complex. The isolated heart is depressed (Salant *et al.*, 1917).

Renal Action.—Underhill, Wells and Goldschmidt, 1913, and Pearce and Ringer, 1913, found that Rochelle salt produces marked renal changes when given hypodermically in doses of 0.25 Gm. per kilogram to phlorhizin rabbits; somewhat larger doses caused the same changes without phlorhizin. Oral administration also produced nephritis, with doses of 3 Gm. per kilogram. Five Gm. per kilogram was fatal in fasting animals. The toxicity is not so great in well fed animals; when diarrhea occurs; or when alkalis are administered. Acetates, citrates and carbonates do not produce these renal changes. Analogous effects occur in dogs. The *epithelial changes* are confined mainly to the convoluted tubules, with some extension to Henle's loops. The glomeruli and interstitial tissue are intact. The lesions result in retention of the tartrate, so that only traces are excreted by the urine even on intravenous injection. In the acute nephritis of rabbits, the *phthalein excretion* is materially diminished. In chronic cases, the excretion again improves somewhat with time. The nitrogen excretion is scarcely altered (Underhill and Blatherwick, 1914). *Hippuric acid synthesis* is not impaired (Kingsbury and Bell, 1915). The excretion of injected *urea* and the excretion of N and dextrose in phlorhizin animals are hindered, but the NaCl excretion is normal (Baer and Blum; Underhill, 1912). The restoration of the blood volume after injection of saline solution is delayed (Bogert, Underhill and Mendel, 1916). The *vascular reactions* of the kidney in dogs are practically unaffected by the tartrate nephritis. The diuretic response to caffeine is somewhat diminished (Karsner, 1917).

Diet on Nephritis.—With rabbits, but not with cats, the diet has a marked influence on the resistance to tartrates. The toxicity is highest when rabbits are fed with oats, hay or cabbage; considerable protection is conferred by food rich in sugar, especially by young carrots. The factors involved have not been differentiated (Salant and Swanson, 1918).

Habituation.—Continuous administration of tartrates to rabbits somewhat increases the tolerance; citrates and oxalates lead to cumulation (Salant and Swanson, 1918).

Potassium bitartrate has been recommended as *dusting powder for rubber gloves.* These may be sterilized with 15 pounds of steam for fifteen minutes, without injury. Higher or more prolonged heat is deleterious.

PREPARATIONS.—***Potassium and Sodium Tartrate,** U.S.P. (Rochelle Salt); $KNaC_4H_4O_6 \cdot 4H_2O$; occurs as a white powder or colorless crystals of cooling saline taste. Freely sol. in water (1:1). Dose, 8 to 15 Gm., 2 to 4 drachms. *Potassium Bitartrate,* U.S.P. (Cream of Tartar); $KHC_4H_4O_6$; sparingly sol. in water (1:165). Dose, 1 to 4 Gm., 15 to 60 grains. *Tartaric Acid,* U.S.P., $C_2H_2(OH)_2(COOH)_2$, is freely sol. in water or alc. *Compound Effervescent Powders,* U.S.P. (Seidlitz Powders), are dispensed in two papers; the blue, Pot. et Sod. Tart., 7.5 Gm. and Sod. Bicarb., 2.5 Gm.; the white, Tartaric Acid, 2.2 Gm. The contents of the white and blue paper are each dissolved in a fourth of a tumbler of water, and these solutions are mixed and administered when the effervescence begins to subside.

Sodium fumarate, $NaO_2C.\ CH{:}CH.\ COONa$, acts as saline laxative with about the same potency as the tartrate, and without renal injury in animals. In man, 10 Gm. cause a bowel movement in the average of six hours, in about three-fourths of constipated patients (H. Gold and Zahm, 1943).

Sodium hydroxyacetate(glycollate), $CH_2(OH).\ COONa$, has a nephrotoxic action similar to tartrate, with prolonged oral administration to cats. Dogs are more tolerant (S. Krop and Gold, 1945).

MAGNESIUM COMPOUNDS

The magnesium ion depresses all nervous and muscular functions, and this even in very dilute solutions (1:25,000). The salts of magnesium are relatively little absorbed, however, and therefore act as osmotic cathartics. With magnesium sulfate, both ions have this effect, so that it is particularly effective. Magnesium oxide and carbonate act also as alkalis. Being very sparingly soluble, their antacid action extends into the intestines, with but little interference with the stomach. They are converted in the alimentary tract into the soluble and therefore cathartic magnesium bicarbonate. MgO (magnesia) is preferred to the usual alkaline carbonates when the stomach should not be burdened with CO_2 gas. It is therefore the best antidote against poisoning by acids. A fair amount of magnesium is absorbed by the alimentary canal, so as to produce some diuresis, but not sufficiently to cause toxic effects, unless large doses of a concentrated solution are taken. When injected hypodermically or into the circulation, it is highly toxic by depressing the heart muscle and the central and peripheral nervous system. It is antagonized by calcium. Magnesium sulfate has been used as a local intraspinal and general anesthetic, and against tetanus, but the effective dose is dangerously close to the fatal (paralysis of respiration), so that its usefulness is limited. A saturated solution of magnesium sulfate is used as a local dressing in *erysipelas* and similar inflammations, but it is doubtful whether it is more effective than other moist dressings.

The *chlorophyl molecule* contains magnesium, somewhat analogous to the iron in hemoglobin (Willstätter).

Normal Occurrence and Requirement of Magnesium.—Magnesium occurs in the body mainly as phosphate and in association with calcium, in the bones, and in larger absolute quantity in the other tissues. The concentration of magnesium in the plasma is about 18 to 34 mg. per liter.

The red corpuscles (Abderhalden, 1898) and striped muscle (Katz, 1896; Huerthle, 1903) contain more Mg than Ca. The ash of bone normally contains 0.8 to 1 per cent of magnesium. This increases with calcium-poor diet, rickets, osteomalacia and fluorosis (Huggins, 1937). The *daily requirement* of adults is generally estimated as 200 to 600 mg.; Duckworth, 1939 (review), considered 200 mg. more nearly correct. Pregnant women probably require 350 to 450 mg. The *ordinary diet* contains 0.19 to 1.2 Gm. (H. C. Sherman *et al.*, 1910). *Children* of four to seven years require at least 13 mg. per Kg. daily; most children of preschool age receive less than the optimal income (A. L. Daniels and Everson, 1936). *Cows, during lactation,* lose considerable Mg, Ca and P, even on a liberal diet. The Mg and Ca loss can not be corrected by the addition of these elements to the diet (Forbes *et al.*, 1917).

Absorption.—When compounds of magnesium are ingested by mouth in food (Forbes and Pitts, 1935) or as medicine, about 30 to 40 per cent is absorbed, practically regardless of the quantity taken, within ordinary limits. The absorption occurs chiefly from the small intestines (Hirschfelder). During their passage through the small intestines, the magnesium salts are mainly changed to the soluble bicarbonate ($MgSO_4 + 2NaHCO_3 = Mg(HCO_3)_2 + Na_2SO_4$). The difficultly absorbable sulfate ion acts independently as an osmotic cathartic. Magnesium oxide, hydroxide and carbonate are first partly converted into chlorides, by neutralizing the gastric acid. The magnesium bicarbonate is likely to form soaps with free fats in the intestine. When Epsom salts and olive oil are given together, this soap may be passed as lumps which have been mistaken for gallstones.

Excretion.—After absorption, and with parenteral administration, the excretion occurs practically exclusively by the kidneys (Meltzer and Lucas, 1907), only in small part from the large intestine. Some is excreted by the bile, in proportion to the amount ingested (Delbet and Bretau, 1931). M. Jacoby claims that in the human subject after parenteral injection of large doses of magnesium against tetanus, the greater part is excreted by the intestines, although its concentration in the urine exceeds that of calcium. A considerable quantity may be retained in the body over two weeks. The urinary excretion of calcium is increased (Mendel and Benedict, 1909). This lessens the lime deposition in young animals (Malcolm, 1905). The *normal human urine* contains 0.2 to 0.3 Gm. of magnesium per day (Nelson and Burns, 1916). The administration of *hydochloric acid* increases the urinary excretion of magnesium, and still more that of calcium (Stehle, 1917; Givens and Mendel, 1917). The *normal food magnesium* is also excreted mainly by the urine (Forbes *et al.*, 1918).

The magnesium content of plasma in clinical conditions was investigated especially by Hirschfelder, 1934. The normal range of magnesium in man, dog and rabbit is between 1.8 and 2.75 mg. per 100 cc. The level in the corpuscles is about twice as high, but is not parallel. If a single dose up to 20–40 Gm. of magnesium sulfate is administered orally to normal persons, the plasma magnesium does not change significantly, although some 40 per cent of the magnesium is absorbed and excreted by the urine within twenty-four hours. In animals, also, the plasma content remains unaltered by corresponding oral doses; but animals with renal injury, either tubular by mercury or glomerular by cantharidin, excrete much less magnesium, and its plasma concentration rises, closely parallel to the phenolsulfonphthalein retention. With kidney excision, and sometimes with mercury nephrosis, the plasma magnesium attains the *coma level*, which normally develops at 17 mg. per 100 cc. with all methods of administration. A single purgative dose administered to patients with kidney disease was found to raise the plasma magnesium to 9–11 mg. in four to six hours, and the patients became drowsy, and some slightly comatose. It may be assumed that repeated doses would reach the actual coma level, and that some "nephritic" comas have been really magnesium coma. It seems advisable, therefore, to administer sodium sulfate rather than magnesium, if saline catharsis is indicated in nephritis. A relatively small rise of magnesium level, by 5 mg., also renders animals much more sensitive to the depressant actions of morphine.

The *magnesium content of red blood corpuscles* is higher than that of the plasma in all animals studied, except beef (Eveleth, 1937). For man (healthy young adults), D. M. Greenberg *et al.*, 1933, found the averages (mg. per 100 cc.) as: plasma 2.74 ± 0.3; whole blood, 4.55 ± 0.38; corpuscles, 6.61 ± 0.53. The content of cells and plasma varied independently. Expressed in milliequivalents per liter, the average for human blood serum is 1.6 (range to 2.2); for corpuscles, 4.6 (3.5 to 6.2) (Hald and Eisenman, 1937). *The tissue distribution of magnesium* after intravenous injection of the sulfate in dogs, resembles that of Na rather than K, being confined practically exclusively to the extracellular fluids for several hours (P. K. Smith *et al.*, 1939).

Low plasma-magnesium levels (1 to 1.5 mg. per 100 cc.) were found by Hirschfelder in ten patients, who showed convulsions or twitchings; two of these were parathyroid tetany. Patients with *essential epilepsy* also had low plasma magnesium, 1.7 mg. or less, during the attacks, with normal values in the intervals. The plasma potassium was doubled during the attacks. Oral administration of magnesium sulfate, 2 Gm. four times daily, did not decrease the convulsions; but these were generally inhibited if 30 Gm. were given by rectum and 1 Gm. intramuscularly (Hirschfelder and Haury, 1936). Earlier workers had also found the plasma magnesium low in many cases of *parathyroid deficiency*, but not in all. In parathyroidectomized dogs, magnesium administration, even orally, helps to prevent tetany (W. F. Wermer, 1927).

Dietary magnesium deficiency is induced in rats by food in which the Mg content has been reduced to less than two per million of dry food. The effects begin in three days, are marked in eleven days and are fatal in 80 per cent of the animals, after an average of thirty-five days. They comprise: *Cutaneous changes:* hyperemia, rough sticky coat, loss of hair, hemorrhages, eschars, exfoliation, lacrimation and salivation. *Erethismus:* the animals are nervous and easily startled, progressing till tonic and clonic convulsions occur spontaneously or on slight stimulation. *Nutritional disturbances:* retarded growth, emaciation, cachexia, occasionally edema of the feet. Marked visceral degeneration, especially in the kidneys, less often in the liver, some in the heart. The *teeth* lose calcium after some two or three weeks, then the peridental tissue. Deficiency extending over six weeks caused degeneration of the enamel epithelium (Becks and Furuta, 1942). The *bones* become heavy with increased content of Ca and P (E. V. McCollum, 1931; Kruse, Schmidt and McCollum, 1933; Orent, Kruse and McCollum, 1934; Brookfield, 1934; Greenberg, Anderson and Tufts, 1936; Schrader, Prichett and Salmon, 1937). A portion of the skeletal magnesium is mobilized (Duckworth *et al.*, 1941). Extensive calcium deposition occurs in the endocardium and aorta and in large arteries and veins, in calves. The percentage of calcium is increased in the heart, kidneys and muscle of rats (Duckworth, 1939). *If the deficiency is less marked* (food of 1 to 2:100,000), convulsions occur only on rather strong stimulation. The nutritional changes can be prevented by providing liberal vitamin G. The magnesium of the body, and its concentration in the plasma, fell to about a third that of the litter controls. With food of 5:100,000, the rats can be carried through pregnancy and lactation (Greenberg and Tufts, 1935).

Magnesium Administration on Bones and Rickets.—In rats with adequate Ca and P income and suitable Ca:P ratio, excess of Mg income to ten times the optimal has no deleterious effects on the growth or ash content of the bones. It is also without effect with a Ca-poor diet; but with a low P or excessive Ca income, increase of dietary Mg has a favorable effect on the mineral content of bone (Rogozinski and Glowczynski, 1934), and the addition of Mg to McCollum's rachitic diet lessens the incidence of rickets (von Euler and Rydbom, 1931). Guinea pigs on diets deficient in vitamins C and D survive longer if magnesium chloride is added (Delbert and Palios, 1929). Mg salts activate bone phosphatase (Jenner and Kay, 1931).

Cathartic Action.—*Magnesium sulfate* is employed as laxative in doses of 2 to 10 Gm., 1 to 2 drachms, in dilute solution; and especially as hydragogue cathartic in doses of 10 to 15 Gm., 2 to 4 drachms, in concentrated solution. The dilute solution may be mixed with $NaHCO_3$, but not with Na_2CO_3. It may also be given as an effervescent salt. *Solution of Magnesium Citrate* is a pleasantly flavored and effervescent draught, dispensed in bottles containing 350 cc. The dose is from $\frac{1}{4}$ to 1 bottle. An enema of magnesium sulfate, 60 Gm., glycerol, 30 Gm., and water q.s. ad 120 cc., is an effective purgative (Fantus). *Magnesium carbonate* and the oxide are administered as powder, $\frac{1}{4}$ to 2 Gm., 5 to 30 grains. "*Milk of Magnesia*" (Magma Magnesiae) is a suspension of magnesium hydroxide, used as a laxative in doses of 1 to 4 teaspoonfuls; and as alkaline dentrifice.

Mechanism of Catharsis.—The available data indicate that this is due to the distensive stimulus of the retained fluid. The direct effects of magnesium on intestinal muscle appear to be purely depressant, but ordinarily this is overbalanced by the mechanical stimulus. The depression is seen especially in excised intestine, and with intravenous or hypodermic injection, where it antagonizes excessive peristalsis induced by ergot, physostigmine or barium (Meltzer and Auer, 1906); but it may also be demonstrated by perfusing isotonic magnesium sulfate solution through the lumen of the intestines of living animals (Sollmann and Rademaekers, 1925). The tone and peristalsis are decreased more markedly than the pendulum movements, and the normal propulsion of the contents is therefore diminished by all effective doses (contrary to the suggestion of Meltzer, 1914). In conditions of excessive tonus or spasm of the intestines, however, magnesium may result in increased propulsion, by relieving the spasmodic closure. This may explain its special usefulness in colics; for instance, in chronic lead poisoning.

The sensitiveness of the intestinal muscle to magnesium is high: 1:25,000 of magnesium salts, *i. e.*, half of the plasma concentration, is distinctly depressant to the excised intestines; but the zone of action is wide, so that the pendulum movement may still be quite vigorous in 1:1250 (Rademaekers and Sollmann, 1924). For the lumen of the intestines of living animals the concentrations must be much higher, because the magnesium ions are but slowly absorbed, and are rapidly diluted by the blood stream before they reach the muscle. However, isotonic solutions (3.5 per cent) are definitely, though only slightly, depressant (Sollmann and Rademaekers, 1925).

Very large doses of magnesium oxide increase somewhat the movements of the human *stomach* (W. H. Dickson and Wilson, 1924).

Duodenol Bile Reflex (*Meltzer-Lyon Test*).—The magnesium sulfate relaxes the tonus of Oddi's sphincter when 40 cc. of 33 per cent solution are administered by duodenal tube; this leads to evacuation of the gallbladder.

The duodenal contents contain at first little or no bile; shortly after, they contain a light yellow bile, and a little later, a darker and more viscid bile, the so-called "B" bile. B. B. V. Lyon, 1919, 1922, assumed that the latter comes directly from the gallbladder, as suggested by S. J. Meltzer, 1917, and believed that its content of pus cells, bacteria, crystalline material, and so forth, reflects the condition of the gallbladder, and that repeated "drainage" by this means would be beneficial in cholecystitis. A similar flow of bile is produced by a variety of substances; for instance, by hypertonic salt solutions in general; by 0.5 per cent HCl; by egg yolk; and by 5 per cent peptone. The latter is preferred by some clinicians as less irritant than the magnesium test (E. A. Boyden *et al.*, 1943).

Application of magnesium to the duodenal surface relaxes Oddi's sphincter (Reach, 1924), and this is sometimes, though not always, followed by evacuation of the gallbladder (Matsuo, 1924); but the bile may also be increased if the gallbladder has been excised (Dunn and Cornell, 1921), or the cystic duct ligated (Mendenhall *et al.*, 1926). This is probably due to the diminished resistance to the bile flow, and not to hepatic stimulation, as was suggested by Einhorn, 1921, but it makes it uncertain whether, in a given case, the bile comes from the liver or the gallbladder (at least unless the test is used in conjunction with the injection of dyes, as suggested by Matsuo). Therapeutically, the "drainage" could scarcely be made sufficiently thorough or frequent to be of material value in cholecystitis.

Isolated bronchial muscle is relaxed by magnesium (Trendelenburg, 1912; Sollmann and Gilbert, 1938).

Systemic actions of magnesium do not ordinarily occur when magnesium salts are taken by mouth, because of the relatively slow absorption and the rapid excretion. However, toxic effects may follow on large doses of the sulfate, and more readily of the nitrate (Meltzer, 1907; C. Fraser, 1909), particularly if kidney injury interferes with elimination (Hirschfelder, 1934). Fatalities have also occurred from enemas (D. W. Fawcett and Gens, 1943). They are most frequent with hypodermic or intravenous injection. They consist in muscular and nervous depression or paralysis. The chief phenomena are analgesia, anesthesia, paralysis of the respiration; and with intravenous injection, direct paralysis of the heart. The motor depression is useful in the symptomatic treatment of traumatic tetanus, but great caution is necessary to obviate respiratory paralysis. The analgetic action is not sufficiently marked, with safe doses, to be useful in itself. It has been employed in obstetric practice to reinforce the analgetic action of morphine and ether, but is ineffective.

Intravenous injection produces immediate and severe, often fatal, depression of the heart and central nervous system. The effects resemble those of potassium, but this acts more on the heart; magnesium, on the respiration. The effects are also seen in blood pressure experiments if the magnesium sulfate solution of the manometer inadvertently enters the artery. The first and most constant result is a *fall of blood pressure*, noticeable before the magnesium concentration of the serum has reached 5 milliequivalents per liter (6.1 mg. of Mg per 100 cc.), and continuing progressively till death. The blood vessels are markedly dilated. The *pulse rate* rises up to 5-7 m. eq. per liter, then declines. The PR interval increases progressively. *Death* occurs from cardiac arrest before 27 to 38 m. eq. per liter (with artificial respiration), occasionally at 15 to 17 m. eq. per liter, simultaneously with the failure of natural respiration, which usually occurs at 17 to 27 m. eq. l. or 18 to 31 mg. per 100 cc. (R. M. Moore and Wingo, 1941; review, P. K. Smith *et al.*, 1942, serum magnesium concentration and effects). With abrupt injection, the heart may be arrested instantly. If the effect is not fatal, recovery occurs quickly, since excretion is rapid.

Cardiac effects are serious only with doses that produce respiratory arrest (A. W. Winkler *et al.*, 1940). They consist in slowing with moderate dilatation; then incoordination; then sudden dilatation and standstill. The arrested heart is in good tonus and responds well to mechanical stimulation (Rothberger and Zwillinger, 1936). The heart may be kept beating by electric stimulation, by stimulation of the accelerators, and by epinephrine (Matthews and Brooks, 1910). Small doses (10 mg. of $MgCl_2$ per Kg.) augment the accelerator response of the heart to epinephrine, but not the response of the heart to direct faradic stimulation (Hazard and Wurmser, 1931).

Paroxysmal tachycardia is arrested immediately by slow intravenous injection of 15 to 20 cc. of 20 per cent solution of magnesium sulfate, without untoward effects (L. Zwillinger, 1935: L. J. Boyd and Scherf, 1943). This also prevents ventricular tachycardia by strophanthin or barium, or converts it into cardiac arrest (Rothberger and Zwillinger, 1936).

Estimation of Circulation Time.—A complex solution containing 42 per cent of magnesium sulfate and 16 per cent of calcium gluconate has been used intravenously. A wave of heat sensation sweeps over the body, and its arrival at any location is timed (Spier, Wright and Saylor, 1936). The sensation is perhaps due to the osmotic action of the hypertonic solution.

Respiration.—The cessation is due mainly to the curare action, the center being ordinarily not paralyzed except with considerably larger doses (Matthews and Brooks, 1910).

Deglutition.—Graded doses paralyze the central mechanism before the peripheral (Auer and Meltzer, 1916).

Curare Action.—This was discovered by Jolyet and Cahours, 1869, and has been confirmed by Guthrie, Meltzer and others (Bresnan and Boyd, 1937). Meltzer and Auer, 1906, found that, like curare, it antagonizes the physostigmine twitchings. Further antagonisms to physostigmine were studied by Joseph, 1909. The curare effect is also antagonized by Ca, K, acetylcholine and epinephrine. The resemblance to curare is not complete, for the threhold of stimulation is also increased in denervated skeletal muscle of dogs (Maaske and Gibson, 1939). Magnesium ions suppress the calcium ion activation of the adenosine triphosphatase of myosin (G. D. Greville and Lehmann, 1943). In spinal dogs, the flexion reflex is abolished (through a central action) by smaller doses than those required to abolish response to motor-nerve stimulation (G. W. Bryant *et al.*, 1939). In intact animals the corneal reflex is the least, the tendon reflexes are the most sensitive to magnesium; the latter are suppressed when the plasma concentration reaches 6 to 14 m. eq. l. The suppression of reflexes by magnesium is due to neuromuscular block, but the anesthetic action is central (H. E. Hoff *et al.*, 1940).

Temperature **is lowered in rabbits by magnesium injection, parallel to the paralytic action, but preceding the latter. It is an independent phenomenon, for it occurs also** if the narcosis is prevented by calcium (Schuetz, 1915, 1916).

Effects on Urine Ions.—The injection of magnesium chloride causes a marked rise of urinary acidity; the phosphate excretion is only slightly increased (C. Mayer, 1917).

Renal Irritation.— The intramuscular or intravenous injection of magnesium salts or sulfates into dogs causes the appearance of *hyaline casts* in the urine. There are no other casts, albumin or other signs of nephritis (Gates and Meltzer, 1914). These occur also when toxic doses of magnesium are injected into the ligated small intestines (Gates, 1914).

Glycosuria.—Parenteral injections produce moderate hyperglycemia and glycosuria. Underhill and Glosson ascribed these to asphyxia; E. Hirsch, 1915, to narcosis and asphyxia; but Kleiner and Meltzer, 1916, found them even with artificial respiration. On the other hand, Airila and Bardy, 1915, stated that intravenous injections of magnesium inhibit epinephrine glycosuria and clinical diabetes, presumably by depression of the sympathetic system.

Magnesium Anesthesia.—Meltzer and Auer (1905) found that a general anesthesia, with abolition of reflexes, may be produced by the subcutaneous injection of magnesium salts (1.5 Gm. of crystalline magnesium sulfate per kilogram of body weight, used as 25 per cent solution). The injection causes but little pain, since the magnesium is also a local anesthetic. The anesthesia is complete in half an hour or an hour, and lasts about two hours. The blood pressure is but little lowered; there is some diuresis, but no diarrhea. Recovery is perfect. Somewhat larger doses are fatal, paralyzing the respiration before the heart. Analgesia is produced when the serum level of magnesium reaches 15 mg. per 100 cc; surgical anesthesia with 23 mg.; respiratory arrest with 33 mg. (R. M. Moore and Wingo, 1942). The effective dose approaches the fatal so closely that this method is not generally advisable for man. Gwathmey, 1921, 1925, in his obstetric anesthesia, used two or three intramuscular injections of 2 cc. of 50 per cent magnesium sulfate with the intention of reinforcing the rectal ether-oil anesthesia; but these raise the plasma magnesium at most to 3 mg. per 100 cc., and no symptoms of depression appear below 5 mg. (Neuwirth and Wallace, 1929). Nor is there any notable potentiation with ether or morphine; their effects are simply additive (Beckman, 1925). Magnesium abolishes the tetanic contraction induced by oxytocic drugs in gravid human uterus (Abarbanel, 1945).

Magnesium produces direct sensory paralysis, both central and peripheral. Meltzer and Auer found that, with proper dosage, it is possible to secure anesthesia when the asphyxial factor is entirely excluded and the muscles are still responsive; although the curare effect may contribute to the immobilization (Guthrie and Ryan, 1910). Careful *intravenous injection in human subjects* (Peck and Meltzer, 1916) produced unconsciousness and complete surgical anesthesia, with incomplete motor paralysis. The *alkali reserve* modifies the degree of narcotic response in rabbits; it is increased by injection of sodium bicarbonate, and decreased by hydrochloric acid (Martini, 1934).

Local Anesthesia.—Meltzer and Auer, 1906, maintained that concentrated solutions paralyze exposed nerve without previous stimulation. Liljestrand, 1909, and Guthrie and Ryan, 1910, claimed that the paralysis is preceded by stimulation.

Spinal anesthesia by lumbar subdural injection of 1 cc. of the 25 per cent solution of magnesium sulfate produces sensory and motor paralysis of the legs and pelvic region, occurring in three to four hours, and lasting eight to fourteen hours (Meltzer and Auer, 1909). There is also retention of urine for one or two days. *Untoward results have occurred.*

Use Against Convulsions.—Injection of magnesium salts is effective against various convulsions (Seremini, 1929), by depression of the neuromuscular junction; but potent doses may arrest respiration and make it necessary to resort to artificial respiration and physostigmine or calcium injection.

Magnesium suppresses *strychnine spasm* (Underhill and Wood, 1929), but other anesthetics, especially barbiturates, are safer and better. In *traumatic tetanus* it is perhaps more effective in relatively small doses (Auer and Meltzer, 1919). It is used in combination with antitoxin. Kocher considered it the best remedy in developed cases. The relief is temporary, so that the injections must be repeated at least daily. It is used to control therapeutic metrazol convulsions (P. K. Smith *et al.*, 1942), and has some value against the twitchings and convulsions of advanced chronic nephritis and eclampsia, although the effects are not dramatic (Winkler *et al.*, 1943).

Administration in Tetanus.—The doses refer to crystalline magnesium sulfate (Kocher, 1915; Meltzer, 1916). *For slight initial symptoms, hypodermic* injections may be used, 1.2 cc. of a 25 per cent solution, per kilogram of body weight, three to five times daily. This has been continued for six to eighteen days without damage. It causes but little irritation. It is safe, but not sufficiently effective for severe cases. In these, the salt may be used *intramuscularly,* 0.6 cc. of 25 per cent per kilogram, six times daily. *Intraspinal injection* uses 1 cc. of 25 per cent per 20 pounds of body weight (0.1 cc. of 25 per cent per kilogram), by lumbar injection. This gives prompt relief, generally lasting twenty-four hours, when the procedure may be repeated. If the respiration should become depressed, the solution should be washed out of the canal. *Intravenous administration* of suitable doses appears safe, injecting 2 per cent solution of magnesium sulfate crystals ($MgSO_4 . 7H_2O$), 500 cc., during thirty to sixty minutes; the action is brief, but the injection may be repeated after a few hours, to a total of not more than 1000 cc. in twenty-four hours; for after two injections the serum concentration may depress the central nervous system. This dosage produces cutaneous vasodilatation. The blood pressure falls in patients with acute nephritis or eclampsia, but not with chronic cardiovascular disease (Winkler *et al.*, 1943).

In *asthmatic crises,* in which epinephrine, ephedrine and atropine have failed, immediate sedation is obtained by slow intravenous injection of 10 to 20 cc. of 10 per cent of magnesium sulfate, but the relief is transient and the injections must be repeated (Rosello and Pla, 1936).

Treatment of Magnesium Poisoning.—When using effective doses of magnesium, the physician should be prepared to combat failure of respiration, by artificial respiration, together with physostigmine (1 to 2 mg. hypodermically) or calcium chloride, 0.02 per cent in normal saline, intravenously, to 600 cc. Extra caution must be used in children. The doses of magnesium should generally be somewhat smaller, supplementing them if necessary by ether or the aliphatic hypnotics. Morphine potentiates the respiratory depression, and should therefore not be combined with magnesium (Issekutz, 1915). The administration of liberal quantities of water, to induce diuresis, would be useful especially in subacute poisoning (Meltzer, 1907).

The **antagonism of magnesium and calcium** was mentioned in the general discussion. *Oxalates* enhance the action of Mg, presumably by removing the antagonistic effect of the tissue calcium. On the other hand, small doses of Mg reduce the toxicity of oxalate, by diminishing the overstimulation (Gates and Meltzer, 1913, 1917). It extends to both central and peripheral actions, including the curare effect (G. W. Bryant *et al.*, 1939). Magnesium narcosis can also be antagonized by intravenous injection of KCl, RbCl, NaCl or LiCl, in descending order of efficiency (A. D. Hirschfelder, 1929). Sodium citrate is also antagonistic (Sollmann).

Magnesium against erysipelas and other inflammations was introduced by H. Hucker, 1907 and 1908. A thick compress (15 layers of gauze) is immersed in a 10 per cent to saturated solution of $MgSO_4$, applied to the inflamed region, covered with oiled silk, and renewed every two hours (Choky, 1911). It is claimed that this subdues the inflammation, the pain, swelling and temperature, if applied in cellulitis, arthritis, epididymitis and similar conditions, and its use has been suggested particularly for facial erysipelas. It probably acts merely by its water content, *i. e.,* like any evaporating lotion; but its high osmotic concentration prevents maceration of the skin, draws fluid from edematous tissue, and washes off detritus from ulcers. It is also somewhat anesthetic to open surfaces.

Delbet and Karajanspoulo, 1915, claimed that intravenous injection of magnesium chloride (dogs, about 15 cc. of 1.21 per cent anhydrous, per kilogram) greatly increases *phagocytosis.* It does not inhibit the migration of leukocytes from the inflamed mesentery of frogs (Ikeda, 1916).

Tumor Growth.—Itani, 1919, failed to confirm any effect on experimental tumors; but Sugiura and Benedict, 1935, reported that a diet deficient in Mg decreases the growth of the tumor; these resume growth if magnesium sulfate is added, and are indeed slightly accelerated by high Mg diets.

Magnesium Sulfate as Insecticide.—V. B. Haber claimed that spraying with solutions of this salt is effective against moths and various other insects, and that grasshoppers are killed by bait containing 20 to 25 per cent of magnesium sulfate. Controlled tests, however, show that it is ineffective (N. F. Howard, 1937; R. C. Smith, 1937).

Inhalation of fumes of magnesium oxide, as generated by the burning of metallic magnesium ribbon or foil, produces fever and leukocytosis, as do the fumes of zinc oxide and other metallic oxides, but less readily (Drinker, Thomson and Finn, 1927).

Metallic magnesium, as used in surgery, dissolves slowly with the formation of magnesium hydroxide and hydrogen gas (Fromherz, 1909). These produce alkali necrosis and mechanical gas trauma, resulting in granulomatous reactions which compress adjacent tissue and cause degenerative changes (R. Z. Schulz and Water, 1942). S. F. Meek *et al.*, 1942, attribute the necrosis to proteolytic action. Inhalation of finely powdered magnesium does not produce gas tumors, since the hydrogen is not confined (L. U. Gardner and Delahant, 1943).

PREPARATIONS.—***Magnesium Sulfate,** U.S.P. (Epsom Salt); $MgSO_4 . 7H_2O$; small prismatic crystals, of cooling, saline, bitter taste; corresponds to about half of its weight of the anhydrous salt; very sol. in water (1:1). A saturated aqueous solution contains about 50 per cent of the crystals, or 25 per cent of the absolute $MgSO_4$. Dose, 2 to 15 Gm., ½ to 4 drachms. ***Magnesium Citrate Solution,** U.S.P., is an effervescent, sweetened and lemon-flavored solution containing a mixture of neutral and acid magnesium citrate, corresponding to about 1.75 per cent of MgO; prepared in bottles of 350 cc., 12 ounces, or 200 cc., 7 ounces, which may be taken as a single dose or be divided. ***Magnesium Carbonate,** U.S.P., hydrated magnesium carbonate, basic or normal; equivalent to about 42 per cent MgO. According to its preparation, it occurs as a more or less bulky powder, "*Light*" or "*Heavy*" *Magnesium Carbonate*, or as white, friable masses, of slightly earthy taste. Practically insol. in water. Average dose, as antacid, 0.6 Gm., 10 grains; as laxative, 2 to 8 Gm., ½ to 2 drachms. ***Magnesium Oxide, Heavy,** U.S.P. (Mag. Oxidum Ponderosum; Heavy Magnesia), is a white, dense, very fine powder; insol. in water. Dose, as antacid, 0.25 Gm., 4 grains; as laxative, 1 to 4 Gm., 15 to 60 grains. *Magnesium Oxide*, U.S.P., *Light Magnesia*, differs from the Heavy in being bulky. ***Magnesia Magma,** U.S.P. (Milk of Magnesia), is a creamy, smooth, aqueous suspension containing about 8 per cent of $Mg(OH)_2$; 0.1 per cent of citric acid may be added, and it may be flavored with aromatic oils. Dose, antacid, 4 cc., 1 drachm; as laxative, 15 cc., 4 drachms. *Tribasic Magnesium Phosphate*, $Mg_3(PO_4)_2O. 5H_2O$, is a white powder, almost insoluble in water, readily sol. in dilute acids. Dose, 1 to 5 Gm., 15 to 75 grains. It is used as antacid, avoiding systemic alkalization. It may be laxative.

SODIUM PHOSPHATE

This name is used in medicine and pharmacy for the disodium salt, Na_2HPO_4. The dihydrogen salt, NaH_2PO_4, is official as "sodium biphosphate," and since it is of feebly acid reaction, it is also called "acid sodium phosphate." The disodium salt is a feeble alkali. Both salts have considerable buffer value, and together they help to maintain the normal reaction of body fluids, especially of the urine. The phosphate ion is relatively nonabsorbable, so that sodium phosphate is a typical saline cathartic. The biphosphate is also cathartic, but produces more local irritation because of its acidity. It is administered to increase the acidity of the urine, especially to permit the liberation of formaldehyde from methenamine (Hanzlik and Collins, 1913). Sodium phosphate does not alter the true reaction of normal urine. The acute systemic effects of phosphates are slight, even on intravenous injection, and quite insignificant on oral administration. The phosphate content of the body has important relations to the ionization of calcium, and therefore to calcium concentration. It is ordinarily maintained at a constant level, and cannot be materially modified by the administration of phosphate. Even parenteral injection is rapidly compensated. Disturbance of the normal phosphate level is a characteristic feature of rickets. Creatine phosphate, hexose phosphate, adenyl pyrophosphate, are essential sources of energy in muscular contraction. Many biological reactions, particularly those involving marked energy changes, depend on phosphorus-containing compounds and frequently involve phosphorus transfer. Co-enzymes generally contain phosphorus (review, C. A. Baumann and Stare, 1939). Phospholipids, especially lecithin (see Index), occur in all living cells, but their functions are not clearly understood.

Use as Cathartic.—A solution of 2 to 4 Gm. of sodium phosphate in a glass of hot water (it is but slowly soluble in cold water) does not have a very disagreeable taste, and when taken before breakfast it usually produces a single soft but not liquid stool, within an hour. It may be administered for considerable periods, without producing habituation.

Effects of Intravenous Injection of Sodium Phosphate.—Moderate quantities act mainly as indifferent saline fluids. They are said to stimulate the vagus endings. Large doses (0.7 Gm. per Kg.) of sodium phosphate (absolute) injected into dogs produce tetany. The Ca content of the blood drops by 40 per cent.

Phosphoric acid injection produces a similar fall of Ca without tetany (C. Binger, 1917; Greenwald, 1918), presumably because the more acid reaction increases the ionization of the calcium.

Pyrophosphates.—Crawford, 1900, found sodium pyrophosphate, $Na_4P_2O_7$, markedly toxic, producing gastrointestinal irritation, hemorrhages and ulcerations; changes in the liver; with continued administration, nephritis and edema. *Metaphosphate*, $Na_4P_4O_{12}$, acted similarly but weaker; the ordinary orthophosphate was nontoxic. Behrens and Seelkopf, 1933, attributed the toxic effects of pyrophosphates and metaphosphates to precipitation of calcium from the blood; K. K. Jones and Murray, 197,3 confirmed that they are antagonized by intravenous injection of calcium salts. *Sodium hexametaphosphate* disionizes calcium without precipitation; indeed, it dissolves most of the insoluble calcium salts. It is reported to be the best solvent for phosphatic renal calculi, *in vitro* (D. R. McCullagh *et al.*, 1941). Blood coagulation is prevented by 1:1000 (C. E. Larson, 1941). It therefore produces the effects of acute calcium deficiency (Jones and Murray, 1937). It is used as a detergent, and for the preparation of a soft-curd milk (C. Schwartz, 1940).

Buffer Functions.—The system Na_2HPO_4:-NaH_2PO_4 functions in the blood plasma and especially in the urine. Its use in Ringer solutions is not satisfactory (Sollmann and von Oettingen), because if CO_2 is removed by aeration, insoluble calcium phosphate, $Ca_3(PO_4)_2$, is formed. The phosphate of plasma is in labile balance with HCO_3 ions, and forms the more soluble $Ca(HCO_3)_2$.

Absorption of Phosphates and Other Phosphorus Compounds.—A considerable but variable fraction of the phosphates is absorbed, mainly from the upper portions of the small intestines (Patwardhan and Nhavi, 1939). The quantity depends partly on the time that the phosphate sojourns in the intestines, as limited by the cathartic action of soluble phosphates; partly on the amount of calcium in the intestines, for this tends to deflect a large proportion of the phosphate to the feces. The insoluble calcium phosphate, administered as such, or as milk, is largely dissolved by the hydrochloric acid of the stomach, so that a part may be absorbed. It is doubtful whether preformed acid phosphate has a material advantage. *Hypophosphites* are absorbed, and for the most part excreted unchanged. *Glycerophosphates* and organic phosphorus compounds are almost completely hydrolyzed in the digestive tract (Plimmer, 1913), and absorbed and excreted as inorganic phosphate (Oeri, 1909), with the same absorption rate (Patwardhan and Nhavi, 1939).

The **excretion of phosphates** occurs by the urine and feces. With a high calcium income, the phosphate is excreted mainly by the feces as calcium phosphate; the urinary phosphates increase with a lime-poor diet (Zuelzer, 1905). "*Phosphaturia*," the deposition of phosphates in the urine, is due to alkaline reaction of the urine, and not to increased phosphate excretion; indeed, the excretion is generally diminished.

When injected subcutaneously, phosphates are rapidly excreted by the intestine and kidneys. The feces contain phosphates even in starvation. The urinary phosphates are generally increased by water diuresis (Baetzner, 1913). They are decreased by increase of plasma Ca, chloralose, epinephrine, insulin and removal of the pituitary body. This is due to a rise of the renal threshold, for the plasma PO_4 may be at normal level (Brull, 1928).

Phosphorus Compounds of Urine.—Practically all the phosphorus of the urine is normally in the form of inorganic mono- and di-hydrogen phosphates. A variable fraction may exist in organic form, as glycerophosphoric and phosphocarnic acid. The organic phosphorus is increased in fasting, chloroform anethesia, morphine poisoning and some pathologic conditions.

Phosphorus compounds of the feces are derived partly from unabsorbed phosphates, from intestinal secretions and from the bacteria. They include various organic forms, nucleins, lecithins, and so forth, as well as calcium and other inorganic phosphates.

PHOSPHORUS COMPOUNDS IN METABOLISM

Occurrence.—Phosphorus compounds make up a considerable proportion of the weight of the body, equivalent to about 0.7 per cent of P (young dog, Heubner, 1914), corresponding to 400 to 450 Gm. of phosphorus for a human adult. It occurs in three classes of compounds: in the bones as insoluble calcium and magnesium phosphate; as soluble phosphate ions in the plasma and other body fluids; as organic compounds, nucleins, phosphocreatine, hexose phosphate, lecithins and phosphatides, in the tissues and plasma. The organic phosphorus compounds of the serum are almost exclusively phospholipids (Greenwald, 1916; Bloor, 1918; Meigs *et al.*, 1919.) About three-fourths of the total phosphorus is in the bones; the muscles contain more than the combined total of the central nervous system, skin, liver and kidneys (Heubner, 1914). Milk contains a considerable amount of phosphorus compounds. (A comprehensive review, with bibliography, is given by Forbes and Keith, 1914.)

The *source of phosphorus* is almost entirely the inorganic phosphates of the food, from which all classes of phosphorus compounds in the body can be constructed. Animals which receive an adequate supply of inorganic phosphates require little, if any, organic phosphorus compounds (review, Marshall, 1915). The presence of some organic phosphorus in the food appears to favor nutrition; but this is probably due to contamination with vitamin (see Index, Lecithin).

Addition of radioactive phosphate to the ingested phosphate shows that it is distributed through all organs, including bones and teeth, so that these must be continually renewed. This also holds for phospholipids, which are built up from PO_4 (Chievitz and Hevesy, 1935). With parenteral administration it passes from the blood through the dentine into the enamel of the teeth; a small amount also from the saliva through the enamel to the dentine (C. B. Barnum and Armstrong, 1942). In the bony tissues of rats, the radioactive P is deposited chiefly in the epiphyses and in the roots of the incisors; but some is found also in the incisor tips, in the molars and in compact bone. A considerable amount is retained in the bones for more than three weeks (M. L. Manly and Bale, 1939).

Daily Phosphorus Requirements.—Under ordinary conditions, the daily phosphorus excretion of normal human adults is equivalent to about 1.5 to 1.75 Gm. of P, or about 3.5 Gm. of PO_4. This must be replaced by a corresponding income to preserve a balance. The ordinary diet contains about this amount (from 1.52 to 5.88 Gm., average 3 Gm., of PO_4; Sherman, Mettler and Sinclair, 1910). Under special conditions of diet, equilibrium may be preserved temporarily with 0.9 Gm. of P. This is the average daily excretion in fasting.

Phosphorus Balance.—Increased intake of phosphorus compounds is followed by increased elimination: in carnivora mainly by the urine; in herbivora mainly by the feces; in omnivora by either, according to the diet. A portion of the excess is retained, especially in growing animals or after wasting diseases. The retention is diminished by deficiency of calcium or excess of magnesium in the food. The bones constitute important depots for a phosphate reserve. The deposition of phosphate in them is hindered by inorganic acids, calcium-precipitating ions, or high potassium or low sodium content of the ration. Cows during *lactation* lose considerable phosphate. This may be corrected by the addition of bone and calcium carbonate to the food (Forbes *et al.*, 1917, 1918). *Excision of the parathyroids* is followed by marked retention of phosphorus, increasing its concentration in the blood (Greenwald, 1916).

Excess of sodium phosphate, when added to the *diet* of young rats, results in permanent renal lesions, necrosis of the cells of the convoluted tubules, beginning on the first day and reaching a maximum about the fifth day, followed by regeneration of atypical cells (E. M. McKay and Oliver, 1933).

Deficient phosphorus income is not likely to occur under normal conditions, as the ordinary diet suffices, not only for maintenance, but for growth. Deficiency may arise by fasting, by general malnutrition, by injudicious selection of food abnormally poor in phosphate or excessively rich in calcium, and probably during lactation. The deficiency should be easily remedied by taking milk. If the phosphorus income falls below the normal requirement, the excretion and finally the phosphorus content of the tissues are diminished.

The phosphorus of the plasma, both organic and inorganic, varies rather widely and is influenced by the food (Meigs *et al.*, 1919). Its diminution soon leads to disturbances of growth and nutrition, the spongy tissue of the bones being most affected (Masslow, 1914). The bones become soft and flexible when their phosphorus content has fallen by one-sixth (Heubner, 1914). The development of the jaws is markedly retarded (D. Y. Burrill, 1943, dogs). Growth that has been interrupted by phosphorus deficiency is resumed when phosphorus compounds are added. Inorganic phosphates are efficient for their purpose (Osborne and Mendel, 1918).

Rickets involves serious disturbance of phosphate metabolism, reflected by a marked diminution of the *phosphate content of the plasma.* This lies normally between 7 and 9 mg. per 100 cc.; in rickets it falls to 3 or 4 mg. The calcium is but little decreased (Howland and Marriott, 1917). It is also reflected in the impaired calcification of the bones, which consist normally mainly of calcium phosphate. In rickets the cellular tissue proliferates, but the mineral matter diminishes, sometimes to half of the normal. The condition may be induced in young animals by food deficient either in inorganic phosphate (Sherman *et al.*, 1918) or in vitamin D, especially if the Ca:P ratio is 4:1 or higher (or by decreasing the absorption of phosphate by administering alum or beryllium). Animals so prepared may be used to test the effectiveness of antirachitic agents (rats, McCollum *et al.*, 1921; rabbits, Goldblatt and Moritz, 1926). The most effective antirachitic agents are cod liver oil (see Index) and actinic light, but rickets of young rats are also promptly healed without these by diets with Ca:P ration of 1:1 (Karelitz and Shohl, 1927). *Phosphatase* is discussed under Calcium.

Hyperglycemia lowers the PO_4 concentration of the plasma. The oral administration of 100 Gm. of glucose to normal adults induces an average fall of 0.6 mg. per 100 cc. in two to three hours (D. R. McCullagh, 1931).

Contraction of skeletal muscle depends for its energy largely on the cleavage and resynthesis of organic phosphate compounds, creatine phosphate (phosphocreatine, phosphagen), hexose mono- and di-phosphate and adenyl pyrophosphate (review, J. Sacks, 1941), by specific enzyme and co-enzyme systems, which may take alternative paths according to circumstances. The interlocking of these processes with each other and with the lactic acid process is obscure. Phosphorylation processes are also concerned in the energy metabolism of cardiac muscle, of nerve, of the liver, kidney and salivary glands, and in the assimilation of sugar and formation of glycogen (reviews, J. Sacks, 1941; C. F. Cori *et al.*, 1943).

The use of *sodium phosphate to increase muscular energy* was tried in Germany during the first World War with the claim that it diminished fatigue in soldiers, and increased the capacity for work and caused euphoria in miners; and that excess of the phosphate produced sleeplessness and palpitation! The response was presumably due to suggestion, for it does not appear to have been confirmed (M. Morse, 1939; Bøje, 1939). Sodium formate was (seriously) suggested for the same purpose, on the basis that Formica the Ant is an indefatigable worker. The role of phosphate in muscular contraction may appear to furnish a more rational basis; but as phosphate is not destroyed in this use, it is not necessary to furnish an extra supply, unless its income were lastingly deficient, and in that case the bones would suffer, not the muscles.

Use of Lecithin and Other Phospho-Lipids and Nucleins, Glycerophosphates and Hypophosphites as Tonics.—The unfounded assumption that these compounds would be more easily assimilated by the tissues, and particularly by the brain, gave rise to their employment as tonics and "brain food" in all sorts of depressed conditions: scrofula, incipient phthisis and cachexia; neurasthenia and tabes; neuritis and neuralgia, and so on. There is no evidence for the better utilization of these compounds; and in any case the ordinary diet furnishes a free supply of lecithin and other phosphorus compounds, so that it is difficult to see how the small quantities added in the form of more or less expensive medicines could have any other than psychic effects. When the psychic element is excluded, they are ineffective.

Glycerophosphates are absorbed in part unchanged, but for the greater part are decomposed in the intestines into ordinary phosphates (Plimmer, 1913). The excretion is entirely as phosphate. Since lecithin is split into glycerophosphates in the intestines, it was suggested that the direct administration of the cheaper glycerophosphates (especially the calcium salt) should accomplish the same results. However, according to Willstätter, the synthetic glycerophosphoric acid is not identical with that formed from lecithin. The evidence of its usefulness is even less convincing than for lecithin (report, Council on Pharmacy and Chemistry, 1916, J.A.M.A., *67:* 1033). A proprietary compound of glycerophosphates and casein was extravagantly advertised as "Sanatogen." It was a costly food, in no sense superior to ordinary casein, such as cottage cheese (Street, 1914).

Hypophosphites were introduced by Churchill, 1855, against tuberculosis on the theory that phthisis is caused by lack of oxidation and that this would be stimulated by organic phosphorus; and that the hypophosphites would be converted into this "phosphatide element." On the basis of this fantastic theory, they were used considerably as tonics in tuberculosis. The clinical evidence is too indefinite and the experimental evidence is generally negative (Report, Council on Pharmacy and Chemistry, 1916, J.A.M.A., *67:* 760). The hypophosphites are *excreted* rapidly and almost completely unchanged (85 per cent; Marriott, 1916) by the urine (Paquelin and Joly; Boddaert, 1895; Massol and Gammel, 1901); a trace may possibly be oxidized (Delaini, 1911). (Patto, 1910, claimed that only a fraction is excreted unchanged.) They are not diuretic. The unscientific status of the hypophosphites is reflected in the polypharmacal syrups in which they are generally prescribed, such as the Syrupus Hypophosphitum Compositus (dose, 8 cc.), containing five hypophosphites besides quinine and strychnine; there is also an emulsion of cod liver oil with hypophosphites. The hypophosphites are easily soluble in water; dose, 0.1 to 1 Gm.; 1 to 15 grains. *Hypophosphorous Acid,* U.S.P., contains about 31 per cent of HPH_2O_2.

Radioactive dibasic sodium phosphate, an artificially produced isotope (P^{32}), is used as a means of internal therapeutic radiation. It has a half-life of fourteen and a half days, sufficiently short to avoid long-range harmful effects. Its disintegration produces only beta particles which do not penetrate farther than 2 to 4 mm. of tissue. The final degradation product is non-radioactive and harmless sulfur. Injected by vein, about three-fourths is retained at the end of three days; half at the end of a week. It diffuses through all tissues, but rapidly growing cells and leukemic cells absorb it preferentially. Its concentration is relatively high in the liver, kidney, spleen and bone marrow; fat and brain contain very little. Its excretion after intravenous injection is practically entirely by the urine; with oral administration, about a fourth escapes unabsorbed in the feces.

The beta rays are capable of producing profound effects on the bone marrow, and thereby the blood cell formation, with minimal harm to the patient. Its therapeutic results are about the same as with x-ray therapy and avoid the serum sickness. It increases the leukocytes, thrombocytes and red corpuscles, almost always with prompt recovery of the white and slower restoration of the red cells (L. A. Hempelman *et al.*, 1944). The results are palliative rather than curative. It is especially useful in polycythemia vera, producing long-lasting remissions (S. Warren, 1945; B. E. Hall *et al.*, 1945). Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and myeloma do not respond so well as they do to x-ray (E. H. Reinhard, *et al.* 1945; normal tissues, W. R. Platt, 1947).

Radioactive sodium phosphate, NaH_2PO_4, may be administered by mouth or vein, in a dosage of 5 to 10 millicuries (C. C. Sturgis, 1946).

PREPARATIONS.—***Sodium Phosphate,** U.S.P.; dibasic sodium phosphate, disodium orthophosphate, disodium hydrogen phosphate; $Na_2HPO_4 . 7H_2O$; large colorless crystals or granular powder, of cooling saline taste. Freely sol. in water (1:4); practically insol. in alc. Dose, 2 to 15 Gm., ½ to 4 drachms. *Effervescent Sodium Phosphate,* U.S.P., represents about 50 per cent of the phosphate. Dose, 10 Gm., 2½ drachms. *Exsiccated Sodium Phosphate,* U.S.P., has had the water of crystallization expelled by heat. It is about twice as strong as the ordinary phosphate. ***Sodium Biphosphate,** U.S.P. (Sodium Acid Phosphate, Monosodium Orthophosphate, Sodium Dihydrogen Phosphate), contains at least 85 per cent of NaH_2PO_4. Large colorless crystals or granular powder, of saline and somewhat acid taste. Very sol. in water; insol. in alc. Dose, 1 to 1.5 Gm., 15 to 20 grains, in water; repeated every one to four hours until the urine becomes acid. It should not be mixed with methenamine.

ELEMENTARY PHOSPHORUS

Yellow phosphorus (to which this discussion refers, unless otherwise noted) is an active poison producing death by acute hepatitis, with alterations of nitrogen metabolism, and fatty changes of the liver and other organs. The continued administration of small doses modifies nutrition and bone formation, and was formerly used against rickets, but it is not effective, nor safe. Phosphorus acts as such: Its actions are not shared by any of its compounds, which are for the most part harmless. Long-continued exposure to the vapors of phosphorus may produce osteitis and necrosis of the jaw.

Amorphous or red phosphorus is nonvolatile, insoluble, inabsorbable and therefore nontoxic when taken by mouth; but since it may contain traces of ordinary phosphorus (to 0.6 per cent—Blythe), large doses could become toxic. Intravenous injections (Nasse, 1885) produced the effects of ordinary phosphorus, probably by conversion into this form.

Fate.—Yellow phosphorus is practically insoluble in water, but diffuses through this as vapor, and forms a dilute colloidal solution, the "phosphorus water." It is soluble in fats and in bile (Hartmann, 1866), and is therefore absorbed from the intestines and from subcutaneous injections, especially if it is administered in finely divided form. Toxic quantities may be absorbed from the skin (Zernik, 1930), and by inhalation of the vapor. The absorption is slow, and the systemic effects are therefore delayed several days. It is finally *excreted* in oxidized form (hypophosphoric acid, Poulet, 1872), but its *fate* is imperfectly known. Although it oxidizes readily in the air, its oxidation in the blood requires days (H. Meyer, 1881); perhaps it has an inhibitory action on oxidizing ferments like that of hydrocyanic acid (Schultzen and Riess, 1869). During its action it exists unchanged in the organs and in the expired air (Claude Bernard).

Etiology of Phosphorus Poisoning.—Phosphorus is accessible in the form of matches or phosphorus rat and roach paste (which contains 3 to 5 per cent), so that accidental or suicidal poisoning is not uncommon. (Sixteen cases, four fatal, from eating of roach paste are reported by J. S. LaDue *et al.*, 1944.) Infusions of matches have been taken as abortifacients, with serious results. Chronic poisoning of somewhat different character is seen from its fumes, in chemical works and formerly in match factories. This, as well as the poisoning by matches, has been greatly diminished since the introduction of amorphous (red) phosphorus. At present, yellow phosphorus is rarely used in making matches.

Phosphorus Matches.—The first phosphorus friction matches were made by Derosne, in Paris, 1816, but they did not become practical until 1833, when processes for their manufacture were invented in several countries. These all employed yellow phosphorus; each match contained ⅓ to 5 mg., so that 16 could be fatal for an adult. The use of the dangerous yellow phosphorus in matches is now prohibited by law in practically all European countries. In the United States, a prohibitive tax has been placed on their manufacture. *Phosphorus sesquisulfide* is now used in ordinary matches, which strike anywhere. This has a low toxicity; guinea pigs are said to show no effects from doses of 0.3 Gm. per day (Brouardel). The "safety matches" have no phosphorus on the sticks, which are usually headed with Sb_2SO_3, $KClO_3$ and glue· the red phosphorus is on the friction surface coating of the box.

The symptoms of poisoning are peculiar in that they occur in two well defined stages: at first, there is local gastro-intestinal irritation: then more or less complete recovery; then, after two or three days, the phenomena of the systemic actions appear. These are distinguished by fatty enlargement of the liver, intense icterus, and the metabolic changes of acute hepatitis. They extend over several days and generally terminate in death by heart failure. Gastric, syncopal or cerebral phenomena may predominate. About half the clinical cases end in death, usually in four or five days, but recovery may occur even in advanced cases. Cerebral symptoms may last a long time, perhaps because of hemorrhages.

Acute symptoms generally start after some hours with gastric pain and burning, eructations with garlic odor, and finally vomiting, which may be luminous in the dark. Later there is often diarrhea. After twenty-four to thirty-six hours, there is more or less remission of the symptoms, usually of short duration, but it may last two or three days.

The *later phenomena* begin with nausea; then gradually slight icterus; abdominal pain and tenderness; vomiting and soft stools, both often streaked with blood; coated tongue and fetor oris. The symptoms become gradually more severe; within two days the area of liver dulness has rapidly increased; the hepatic region is painful and tender, and the icterus more intense. Icterus is noted in about half the cases; it appears generally on the second to the fourth day, but may be delayed till the twenty-fifth (Jaksch). If death occurs within the first two days of the second stage, there is usually no icterus (Magnus, 1914). All foods and liquids are vomited. The patient becomes profoundly prostrated with insomnia, anxiety, headache, muscle pains, spasm and feebleness. The temperature is normal, the skin dry, the respiration increased, the pulse soft but of normal rate. The *urine* is scanty, acid, dark brown from bile and blood and contains albumin, casts and abnormal nitrogenous substances. Multiple *hemorrhages* may occur as petechiae or in larger areas, in the skin, mucosae, lungs and other viscera.

Agonal Stage.—The pulse becomes thready and intermittent; the heart dilated, with systolic murmurs; the respirat on dyspneic or Cheyne-Stokes. Consciousness may bei undisturbed, but generally there is somnolence, sometimes delirium and disturbances of temperature; finally coma.

Diagnostic postmortem features are: the icterus; phosphorus odor on opening abdomen; blood tarry and difficultly coagulable; multiple hemorrhages; fatty enlargement of the liver and other organs. Gastric lesions are slight or absent. The *mitochondria of the pancreatic cells,* according to W. J. M. Scott, 1916, are the first structures to show changes in phosphorus poisoning.

The *course* runs from two to fifteen, averaging perhaps eight, days. In the fatal cases, death occurs usually before the eighth day, most commonly in four to five days (Jaksch, Tardieu); it has occurred exceptionally in four to eight hours. Serial experiments on rats with a dosage of 4 mg. per 100 Gm. show that the hepatic changes appear in eighteen to twenty-four hours and increase to seventy-two hours. If this time is survived, the liver returns rapidly and completely to normal (Love, 1932). The *fatality* is high, about 55 per cent (Falck); with larger quantities, such as are used for abortion, it may reach 95 per cent (Kobert). The *fatal dose* may be as low as 50 mg., generally about 100 mg.; but 15 mg. may be severely toxic. It is much more dangerous in solution or when finely divided than when larger lumps are taken. Monti administered as high as 7 mg. daily for three weeks against rickets, but this dosage proved toxic. A two year old child has been severely poisoned by therapeutic doses (1.2 mg. distributed over three days; Nebelthau). Magnus, 1914, stated that no dangerous effects have ever occurred (in children up to eight years) from 0.5 mg. per day, although there may be some vomiting at first. He reported the smallest dose that has exceptionally produced dangerous effects as 1 mg. per day.

The *effects on the liver* dominate the picture. They may be summarized as disappearance of glycogen, incomplete combustion of lactic acid, increased excretion of ammonia, increased protein destruction with incomplete desamidization of certain amino acids, fatty infiltration, mechanical interference with bile formation, increased postmortem autolysis, decrease of fibrinogen. The excretion of p.-s.-phthaleine is delayed (Whipply and Sperry, 1915). The liver, heart, ganglion and other nerve cells show degenerative changes similar to those of chloroform intoxication (Lissauer, 1914).

Bile and Icterus.—The swelling and subsequent cirrhosis of the liver obstruct the bile capillaries, so that bile secretion is diminished or suppressed; the gallbladder contains only a little mucous fluid. The retention of the bile constituents produces the characteristic intense icterus. It was formerly believed that the formation of bile was also increased by the destruction of the blood, but there is no evidence for such destruction.

The *coagulability of the blood* is diminished, probably by destruction of fibrinogen or of fibrin ferment, or possibly by the production of peptone bodies from the destruction of proteins (Cevidalli, 1902). Denny and Minot, 1915, also found the antithrombin content of the blood diminished. The *hemorrhagic tendency* is explained by the lessened coagulability of the blood and by the fatty changes in the capillary endothelium. The *ecbolic action* which occurs with fatal doses may be referred to degeneration of the blood vessels. However, phosphorus also passes to the fetus in sufficient amount to produce fatty hepatic degeneration. Lewin records twenty-seven cases in which phosphorus was used as abortifacient; it induced abortion in twenty-three of these, and death of the mother in over half of the cases.

The *action on metabolism* occurs in chronic poisoning, or as a secondary process after a single larger dose. The phenomena consist in increased tissue destruction with disturbances of syntheses, oxidations and dissociations; deposition of fat in the liver; increased but incomplete nitrogen metabolism; interference with glycogen deposition; increased lactic acid and ammonia excretion; inhibition of other synthetic processes. The mechanism is not understood. It appears to involve interference with ferment actions, primarily with some of those involved in carbohydrate metabolism.

Fatty Changes.—Extensive deposition of fat occurs particularly in the liver cells, whose fat content may reach three or four times the normal; but it is seen also in practically all other cellular organs: muscle, skeletal, smooth and cardiac; kidneys; blood vessels; epithelium of stomach and intestine, and so on. The fatty changes are preceded by "cloudy swelling," which is probably an intermediate stage. They are followed by proliferation of interstitial connective tissue (cirrhosis). *Similar fatty changes,* especially in the liver, occur in poisoning by: Phlorhizin, arsenic, antimony, many volatile oils, the alcohol group, chloroform, carbon tetrachloride, benzene, phallin, and the like, in starvation and in diets rich in fats, in experimental diabetes, on injection of anterior pituitary extract, on feeding cholesterol. They may be decreased or prevented by feeding lecithin or *choline.* The latter hastens especially the disappearance of fat from the liver in the recovery phase of phosphorus poisoning. Its mechanism is not explained: histological studies indicate that it does not affect the duration of the degenerative changes in the liver, other than the fat accumulation (C. H. Best, Maclean and Ridout, 1935). The *mechanism of the fatty degeneration* has been studied especially in the liver. It was originally assumed that the fat was formed *in situ,* by true degeneration of the protoplasm of the liver cells (Bauer, 1878). However, Lebedeff, 1883, disproved this, finding that fat is deposited in the liver only if the fat store of the body is ample, and that if some foreign fat is introduced into the subcutaneous tissue, the fat deposited in the phosphorus liver agrees in composition with this foreign fat. This suggests that the liver fat is merely transported from the fat depots. These observations were confirmed by Rosenfeld, 1897; Pflueger, 1898; Foulerton, 1921; and others. (However, Salvioli and Sacchetto, 1922, claimed that the phosphorus increased the visible fat in the liver, even in animals starved to the last degree; but the organ fat had not entirely disappeared.) Similar observations were made in regard to the other poisons that cause "fatty degeneration" of the liver. The conclusion was strengthened by the observation of Athanasiu, 1898, that the total fat of the body is not increased by phosphorus. In fact, it is rather diminished (Shibata, 1911). The increased fat of the liver must therefore have been drawn from other parts of the body so that the process is one of infiltration. Lusk found that the combustion of fat in phosphorus poisoning is not changed. Some of the "fat" consists partly of other lipoids (Dastre and Morat, 1879); Heffter, 1890, claimed that the percentage of lecithin is decreased. The fat in the heart (studied by Rosenfeld, 1906) is also infiltrated (Leik and Winckler).

Autolysis.—In advanced phosphorus poisoning, the postmortem autolysis of the liver is greatly accelerated (Jacoby, 1900; Porges and Pribram, 1908), probably by decreased resistance of the liver cells to the normal autolytic ferments (Wells). Direct addition of phosphorus to excised normal liver does not hasten autolysis (Jacoby).

Tissue cultures from the livers of rabbits poisoned by phosphorus or carbon tetrachloride show the injury by deformed growth and atypical cells (Adlersberg and Minibeck, 1936).

The *nitrogen metabolism* is greatly increased. The urinary nitrogen may rise by 300 per cent (Storch, 1865). The excretion of phosphate and sulfur is also increased, while the chlorides are diminished by the inanition (Welsch, 1905). All the nitrogenous metabolites may participate in the increase (v. Jaksch, 1903), but not to the same extent (Muenzer, 1894). The urea is not nearly so much increased as the others and may even be diminished. It is to a large extent replaced by ammonia. This may be attributed to an increased production of sarcolactic and other organic acids. The uric acid excretion does not show characteristic changes; the creatinine output is scarcely affected (Lusk). The hippuric synthesis of excised kidneys is checked (Hauser, 1895). The blood of dogs poisoned with phosphorus shows increase of nonprotein nitrogen, urea and amino acids, partly through increased metabolism, and partly because of diminished excretion. There is generally a terminal acidosis (E. K. Marshall and Rowntree, 1915, 1918). The total N:urea ratio of the blood rises (Desqueyroux, 1922). The protein cleavage products may play a part in the production of the symptoms (Moriani, 1916).

The appearance in the urine of *amino acids*, leucine, tyrosine, cystine; and peptone-like substances (Schultzen and Riess, 1869) is diagnostically important. Clinical cases may not show the tyrosine. The peptone-like substances are present especially in the early stages. Their nature is not known (Harnack, 1893).

Carbohydrate Metabolism.—The *blood sugar* level is temporarily increased; after large doses, this is followed by severe hypoglycemia (Ivancevic, 1927). The diastase of the serum is greatly increased, with decrease in lipase and no change in protease. These results occur also after excision of the pancreas and are presumably due to the action on the liver (Falkenhausen, 1928). Phosphorus causes the disappearance of glycogen from the liver. This is not due to increased glycogenolysis. Phosphorus must therefore inhibit glycogen synthesis, especially from noncarbohydrate sources (E. Franck and Isaak, 1911; Desqueyroux, 1922). This would explain the prevention of epinephrine glycosuria by phosphorus, and the noncombustion of lactic acid. According to v. Fuerth, 1914, lactic acid appears in the urine only when the rabbits are fed on an excess of sugar. Dextrose is not converted into glycogen (E. Neubauer, 1909), thus explaining the occurrence of glycosuria when carbohydrates are fed. Glycogen may be still formed from levulose. The tolerance for galactose and levulose is lowered (E. K. Marshall and Rowntree, 1915). Phosphorus poisoning disturbs the conjugation of glycuronic phenols by slices of liver; chloroform poisoning apparently does not interfere (E. Bueding and Ladewig, 1939).

The *increase of nitrogen excretion may be due to carbohydrate disturbance.* Franck and Isaak, 1911, believed that this interference with glycogen synthesis is the primary action of phosphorus; they attributed the increased protein destruction to the necessity of making up for the lessened supply of energy material. The fat transportation to the liver could be similarly explained. Accordingly, Rettig, 1914, found that a diet rich in carbohydrates prevents the increased protein catabolism and the fatty changes. Ray, McDermott and Lusk, 1899, also showed that with dogs rendered glycosuric by phlorhizin, phosphorus does not increase the nitrogen excretion, again indicating that the nitrogen excretion is not due to direct destruction of the protoplasm, but is in some way connected with the disturbed carbohydrate metabolism. Lusk, 1907, suggested that the primary action is to inhibit the ferment which burns lactic acid, and that the nitrogen changes are due to the resulting acidosis.

Oxygen Consumption.—The metabolic effects of phosphorus resemble those of oxygen deprivation (*e. g.*, Porges and Pribram, 1908), and it has been suggested that phosphorus renders the cells less capable of utilizing oxygen. However, it is also possible that the metabolic changes in both cases are the secondary result of some other common factor. Indeed, Lusk, 1907, showed that the oxygen consumption is not diminished, but rather is somewhat increased, partly by fever, and probably also by the toxic action of increased protein destruction.

Circulation.—Phosphorus appears to have direct toxic effects on the heart muscle, for the isolated frog heart is depressed by the direct application of phosphorus solutions (Okuto, 1926); with intravenous injection the heart is paralyzed before anatomic degeneration has set in (Meyer, 1881). In the collapse, splanchnic stimulation is ineffective. In clinical poisoning, the syncopal cases may be due to this cardiac paralysis, but generally the circulation suffers but little until the agonal state.

Electrocardiogram changes, similar to those of glomerulonephritis and severe anemia, with recovery, were recorded in a patient by R. A. Dathe and Nathan, 1946.

Muscle and nerve are not directly affected.

The *central nervous system* plays a subsidiary role, but is said to show histologic changes (Rossi, 1897).

Changes in the Blood.—On the basis of experiments on birds (Fraenkel and Roehmann), it was formerly believed that the *red corpuscles* are rapidly destroyed, in man and mammals (Taussig, 1892; v. Jacksch, 1893); no destruction occurs, however, even in severe poisoning. In fact, the corpuscles are often increased (Ragazzi, 1910; Leoncini, 1914), and this is the typical effect of therapeutic doses. The *hemoglobin* is not altered (Leoncini). The viscosity and electrical resistance of the blood are increased by the polycythemia, and remain so until death approaches, when they suddenly decrease. The osmotic pressure of the blood was found increased by Bottazzi, 1896, unchanged by Ragazzi. The *alkalinity* is diminished. The catalase action is moderately decreased (Duncker and Jodlbauer, 1911). The *diastase* of the serum is greatly increased, the lipase somewhat decreased, and the protease unchanged (similar changes follow excision of the pancreas; Falkenhausen, 1928). The statements as to the *leukocytes* are confusing: Ragazzi describes increase of the polynuclears, and disappearance of eosinophils. According to Leoncini, the leukocytes are at first diminished, then sometimes moderately increased.

Local Actions.—Irritation of the mucosae is shown by the early acute symptoms, but phosphorus is not corrosive. *Phosphorus burns* are no more dangerous than other burns of similar extent and do not produce any of the symptoms of phosphorus poisoning. Contact with copper sulfate, in 1 per cent solution, stops fuming immediately (D. D. Walton, 1942).

Treatment of Acute Poisoning.—Any phosphorus remaining in the alimentary tract should be oxidized and removed. In view of the slow absorption of the phosphorus, gastric lavage may be successful even when started two hours after the ingestion. A large quantity of fluid should be used (5 to 10 gallons). Copper sulfate, 0.1 to 0.2 Gm. in water every ten minutes until emesis, acts as a prompt emetic, and meanwhile oxidizes the phosphorus and envelops the globules with a coating of reduced copper which retards absorption (Woehler and Vogel, 1836), but it was not very successful in dogs. Gastric lavage with other oxidizing agents may be substituted: $KMnO_4$, 0.1 per cent (Bokai and Antal; Koranyi, 1889), or H_2O_2, 2 per cent of the official solution. These should be followed by 2 to 4 ounces of liquid petrolatum and a full dose of a saline cathartic. Oils, fats and milk should be avoided while any phosphorus remains in the intestines, since they increase its solubility and absorption. Sodium bicarbonate, glucose and insulin may be given if hepatitis threatens. When the systemic symptoms have set in, these measures are practically useless and the treatment must be mainly symptomatic. Transfusion of blood is said to give good results.

In phosphorus-poisoned animals, the *feeding of sugar* was found to replenish the hepatic glycogen, and to diminish the other toxic manifestations (Simonds, 1919).

Oil of turpentine, 0.5 Gm. several times daily for a week, may be tried (Andant, 1868; Koehler, 1872), but its benefits are doubtful, or at least inconstant. They seem to vary with different varieties of the turpentine, the fresh being often as effective as old ozonized samples. The action is not due to simple oxidation of the phosphorus, but to the formation of complex compounds (Busch and Fischer); Kobert believes that it may be effective even after the phosphorus has been absorbed.

Chronic Phosphorus Poisoning.—This is seen especially in factories using yellow phosphorus and also in the manufacture of phosphor bronze. The most common manifestation is necrosis of the jaw; sometimes bronchitis, to which tolerance is acquired; and cachexia resembling mild acute poisoning. Strict *prophylaxis* should be enforced. The manufacture of yellow phosphorus matches has been prohibited in most civilized countries. Exposed workers should attend to ventilation, cleanliness and strict oral hygiene (Ivy, 1911). Persons with defective teeth should not be subjected to the risks. The literature is reviewed by H. Heimann, 1946.

Necrosis of the jawbone, "phossy jaw," is due, not to a direct action of phosphorus, but to a lowered resistance to infection and defective repair which are induced by the effects of phosphorus on the blood vessels in the Haversian canals of the bone (see below). Identical necroses in the teeth and other bones have been produced experimentally (Wegner, 1872) by prolonged exposure of rabbits to phosphorus vapor, after laying bare the periosteum. The greater liability of the jawbone is due merely to its greater exposure to infection, through diseased teeth and alveoli. Clinically, only a small proportion of the exposed workers, 2 or 3 per cent, develop the necrosis. It may occur several years after the subjects have been removed from exposure to phosphorus, but this generally arrests the advance of the disease. The symptoms begin with salivation and toothache, more often in the lower jaw, with suppurative ulceration of the gums around a carious tooth or generally a root abscess which does not heal after extraction, with suppurating fistula and gradual progressive necrosis of the maxilla. The absorption of the necrotic tissue causes cachexia. The mortality in serious cases is 15 to 20 per cent. Excision of the diseased bone is the only treatment. Large sequestra are now rarely allowed to develop. Caries should prompt removal from exposure (Kennon and Hallam, 1944).

Bone Changes.—Continued administration of small doses of phosphorus to growing animals results in the characteristic "phosphorus band," a layer of dense bone under the proliferating epiphyseal cartilage of the long bones (Wegner, 1872). In adults, the Haversian and marrow canals are gradually filled with dense bone of normal composition and structure (Kassowitz). The densifying effect is probably due to delayed reabsorption of bone tissue from scanty formation of blood vessels. The roentgen and histologic bone and tooth changes have been studied by C. O. Adams and Sarnat, 1940.

This action would not be useful against rickets, as was assumed by Kassowitz, 1884, for it would not accelerate the calcification of cartilage, which is the characteristic deficiency of this disease; indeed, it is possible to produce the two conditions, phosphorus band and defective cartilage calcification, concurrently (A. F. Hess). Phosphorus administration does not even improve the effects of cod liver oil. The densifying action might be of some use in osteoporosis and perhaps in fractures (Phemister, 1918), but the results are not uniform and its use is not advisable, since the effective dose (1 mg. per day in cod liver oil or in pills) may cause some gastro-intestinal disturbance; sometimes the jaw necrosis; and rarely typical phosphorus poisoning. Engelhardt and Winters, 1915, found the pills and spirit fairly stable, but not always. Compound elixirs are less stable.

Growth.—Phosphorus in doses proportional to those used clinically, administered to young rats with their food over long periods, produced marked and progressive retardation of growth. The animals remained stunted even when replaced on poison-free food. This suggests that the failure of growth may be due to premature solidification of bone, but no observations were made in this direction. With $\frac{1}{25}$ of the clinical dosage, there was first a doubtful retardation of growth; but after four months on this dosage the weight increased markedly above the normal, especially in old animals; with young animals this increase occurred when they were replaced on the poison-free food. No observations were made as to the nature of the overweight tissue, or of the metabolism (Sollmann, 1924).

Hepatic *cirrhosis* was reported by F. B. Mallory, 1933, after prolonged administration (five months) of small doses of phosphorus (0.33 mg. per Kg.) to rabbits and guinea pigs.

Phosphorus in Nervous Diseases.—It has been advised as a tonic in alcoholism, neurasthenia, sexual exhaustion, neuralgia, tabes, cerebral degeneration, and the like, and in chlorosis and anemias. There is no scientific support, either experimental or clinical, for this use. *Zinc phosphide* has been suggested as a therapeutic substitute (Vigier, 1876); there is little scientific information about it.

Phosphorus occurs as a translucent waxy substance of distinctive odor. Melts at about 44° C. Oxidizes (ignites!) on exposure to air. Practically insol. in water, but slightly sol. in alc. (1:400). Sparingly sol. in oils. Sol. in fat solvent. Dose, 0.6 mg., $\frac{1}{100}$ grain, as pill or oily solution. These must be recently prepared. Maximum dose, 2.5 mg., $\frac{1}{25}$ grain.

Phosphuretted Hydrogen.—This gas (Phosphine—PH_3, not to be confused with Phosgene, $COCl_2$!) is a violent poison; 0.025 per cent in air is harmful after a time; and 0.2 per cent is quickly fatal, producing dyspnea, fainting, lowered blood pressure, slowed heart; nausea and vomiting; convulsions and paralyses; coma and asphyxia. The symptoms have been confused with those of food poisoning. Slight cases recover without aftereffects. Postmortem examination shows pulmonary congestion and exudation. The blood is not changed (in contrast to AsH_3, arsine). Industrial poisoning occurs from its presence in acetylene and ferrosilicon. Prolonged exposure may produce the ordinary phenomena of chronic phosphorus poisoning (review, S. H. Webster, 1946).

Phosphorus pentachloride poisoning is described by Roch, 1914.

SODIUM CHLORIDE

Sodium chloride constitutes the greater part of the electrolytes of the tissues (with some exceptions), and especially of the fluids, of vertebrates. Its ions are essential for the functionation of most cells. Since the ions are constantly excreted, especially by the urine, they must be constantly replenished, leading to the instinctive use of salt in food. Its administration to mammals, even by intravenous injection, produces practically only osmotic effects; but marked ion actions may be observed by exposing excised tissues to solutions with or without the sodium and chloride ions. The therapeutic uses of salt depend largely on its osmotic effects. These result in stimulation of the gastric mucous membrane, leading to its use as condiment and in some indigestions; under suitable conditions, a laxative action; irritation of the skin, with attending reflex stimulation, utilized as salt-water baths. After absorption, it leads to diuresis and slight metabolic changes. Isotonic solution is used as vehicle or for cleansing sensitive mucous membranes, *f.i.*, the nose; and for hypodermic and intravenous injections. These saline infusions are employed in hemorrhage, collapse, and for the dilution or removal of systemic poisons. The intravenous injection of strongly hypertonic solutions is fatal, with stimulation and paralysis of the central nervous system.

Retention of chloride occurs in certain pathologic conditions, especially pneumonia and other fevers, nephritis, cancer, and so forth. It may favor the formation of edemas, against which salt-poor diet is sometimes efficient. NaCl depletion in pernicious vomiting, excessive sweating and Addison's disease accounts partly for the phenomena of these conditions.

NaCl Capital, Income and Turnover.—The total NaCl of a human adult amounts to 150 to 300 Gm. (Magnus-Levy, 1906), 5 to 10 ounces, averaging perhaps half a pound. The daily turnover depends on the income, and this on the dietary and culinary taste of the individual; 10 to 15 Gm. is a fair approximation for most persons, so that the daily turnover is about a twentieth of the total stock. Reabsorption in the kidneys protects the organism against excessive loss that would lower the plasma chloride below the 0.562 per cent of NaCl, or 0.38 per cent of Cl.

The *daily salt consumption* of a thousand residents of the city of New York was appraised by B. I. Ashe and Mosenthal, 1937, from the urinary excretion, as: less than 4 Gm. in 5 per cent of the individuals; 4 to 8 Gm. in 37 per cent; over 8 Gm. in 57 per cent; over 20 Gm. in 1.6 per cent. A similar distribution obtains for patients with hypertension, with or without nitrogen retention. Reduction of the income to 5 Gm., or even 1 to 2 Gm., causes no disturbance. For *parenteral nutrition*, 5 Gm. should be supplied daily, more for febrile and perspiring patients; that lost by vomiting should be replaced in addition. Verhage, 1940, reports that a *minimal daily increase* of 200 to 300 mg. of sodium, about a fifteenth of the normal, suffices to maintain the normal sodium level of the blood plasma, the excretion being reduced in proportion. Carnivorous animals obtain a sufficient supply in their food; but since K predominates over Na in the ash of plants, herbivora and animals feeding on a mixed diet require additional NaCl. This need has led to the *instinctive use* of this salt: in regions remote from salt deposits, ashes of plants rich in Na have been used by peoples as ignorant as the Negroes of Soudan; the taste is an effective indication of its presence and incentive to its use. It contrasts sharply with the taste of KCl. A table of the salt content of food is given by Leva, Arch. f. Verdauungskr., *16:* 267.

Absorption.—Sodium chloride is readily absorbed, chiefly from the duodenum; but it serves to keep the intestinal contents isotonic, so that its absorption extends to the rectum.

Studies with *radioactive isotopes* show that Na, Cl, Br and I can be detected in the hand within three to six minutes after ingestion; their absorption is complete in three hours. The absorption of K is about half as fast; it appears in the hand in six to fifteen minutes, and its absorption is completed in five hours (J. G. Hamilton, 1938). The isotopic sodium is rapidly distributed into all the regions where it is normally present. Its urinary excretion followed an exponential curve (D. M. Greenberg, Campbell and Murayama, 1940).

The epithelium of the small intestines, like that of the renal tubules, can move chloride from lower to higher concentrations, against osmotic pressure. If an isotonic mixture of NaCl and some relatively indiffusible salt is placed in an intestinal loop of a living dog or cat, it becomes practically chloride free in one and one-half hours. This is not explainable on physical grounds, and is abolished by protoplasmic poisons, such as sodium cyanide, arsenite or fluoride, hydrogen sulfide or mercuric chloride (Ingraham and Visscher, 1936). *Adrenalectomy* in rats decreases the absorption of sodium chloride from the intestines, but not that of dextrose (W. G. Clark, 1939).

The **distribution of salt in the body** is not identical for the Na and Cl ions; but it is convenient to express Cl also as NaCl and this is generally a fair approximation, since Na is the most abundant of the soluble cations. The chloride ion is confined chiefly to the extracellular fluids, as are also the other haloid and related anions (Br, I, NO_3 and SCN).

The *extracellular fluid*, including the blood plasma and lymph, amounting to about 20 or 30 per cent of the body weight, contains practically all the sodium and chloride. A small amount is *intracellular*, for instance in the red blood corpuscles; about a tenth in the skin (Eichelberger *et al.*, 1943), and very little in muscle and liver cells. This does not diffuse readily in either direction (J. P. Peters, 1944). The *distribution of chloride* in different organs and tissues is relatively constant in different individuals of the same species, and remarkably similar in different species (K. A. Winters, 1934). Comprehensive determinations were made by Wahlgren, 1909, and Padtberg, 1920, on dogs. Similar relations probably hold for man and other animsls: the entire body contains about 0.17 per cent, expressed as Cl (0.11 per cent, Rosemann, 1910). Of this about a third is in the skin, the remainder chiefly in the blood, muscles, bones and intestines. Muscle cells contain little or no Cl (Hastings and Eichelberger, 1937). The highest percentage of Cl exists in the skin (0.38 per cent); then the blood (0.31 per cent); kidneys (0.26 per cent); and lungs (0.24 per cent). The brain, bones and intestines contain 0.17 to 0.18 per cent; the liver, 0.13 per cent; the muscles, only 0.07 per cent. According to other determinations, blood serum contains 0.36 to 0.42 per cent (equivalent to 0.60 to 0.64 per cent NaCl); saliva, 0.16 to 0.24 per cent Cl; the human intestinal juice, 0.58 to 0.67 per cent NaCl; sweat, 0.285 per cent (Kovesi); human gastric "appetite" juice, 0.49 to 0.56 per cent Cl (Carlson, 1915). The red corpuscles contain 0.12 to 0.18 per cent of Cl. The chloride content of the entire body is considerably higher in newborn rats than in adults. It decreases markedly in the first two weeks after birth (K. A. Winter, 1934).

The *ionic content of human blood serum*, at its normal reaction of *p*H 7.4, expressed in milliequivalents per liter, is essentially Na (142) + K (5) + Ca (5) + Mg (2) = Cl (105) + HCO_3 (25) + protein (17) + PO_4 (2) + R (5). Hald and Eisenman, 1937, give somewhat lower values for Na, ranging from 129 to 139. *Human erythrocytes* contain much less Na, averaging 16.5 m. equ. l. Their Cl averages 50; the Cl relation to the serum accords with the Gibbs-Donnan equilibrium, so that the corpuscles are permeable to Cl ions. In diseased conditions the Cl' and HCO_3' tend to vary reciprocally (review, V. C. Myers and Muntwyler, 1940).

Artificial Variations of Chloride Content.—Padtberg studied the changes following the *intravenous injection of NaCl.* Here, also, the skin maintains the highest percentage; but because of their greater mass, the muscles and intestines take up the greater absolute amount. Rosemann, 1911, found the entire Cl content increased by 100 per cent when dogs were given *highly salted food.* With the return to normal diet, the Cl content returned to one and one-half times the ordinary level within five days; the further fall to normal occurred much more slowly. *With Cl-poor food*, the total Cl content sinks to 0.137 per cent, the loss being greatest from the skin. The skin therefore acts as a chloride depot, storing and giving off most of the excessive or deficient Cl. Fasting lowers the total blood chloride by 10 per cent, due almost entirely to loss of plasma volume, for the Cl concentration in the plasma and blood cells is almost unchanged (Austin and Jonas, 1918; Bottin, 1934). *By feeding nitrate* with chloride-poor food, the total chloride may be reduced by more than half in a week, the tissues losing chloride generally in direct proportion to the loss of serum chloride (Hiatt, 1939, 1940).

Chloride Content in Disease.—Biernacki, 1894, found the Cl of the blood constant in numerous diseases. Javal and Adler, 1906, determined the percentage of Cl and water in the organs after death from various diseases, with a special reference to edema, but the results were not decisive. Leva, 1915, stated that human organs in renal, cardiac and vascular disease may contain twice, the skin even three times, the normal amount of Cl, without material increase of their fluid. Similar results were obtained on uranium rabbits. *Decreased Cl concentrations of the serum* occur especially with profuse vomiting, diabetic acidosis, acute mercuric chloride poisoning, adrenal cortex deficiency, lobar pneumonia and other fevers (review, V. C. Myers and Muntwyler, 1940). F. C. McLean 1915, found the chloride of the plasma increased, clinically, in cardiac and renal disturbances, and in pneumonia; diminished in diabetes and with diuretics. The chloride and urea content of the plasma do not go parallel. In uremia, the diminution of blood chloride is concomitant with increased hydrogen ion concentration (McLean, 1916).

The **distribution of Na and of K** differs for various tissues, and also for the same tissue in different animals; especially in the *red blood corpuscles* (see potassium). The concentration of Na ranges from 0.16 to 0.22 per cent in most animals, 0.036 to 0.041 in man, and practically none in the horse, pig and rabbit (Streef, 1938), the quantity being practically reciprocal with that of potassium. Intravenous injection of radioactive sodium into dogs showed that their corpuscles are permeable to Na ions (W. E. Cohn and Cohn, 1939). Muscle cells contain but little Na or K (Hastings and Eichelberger, 1937).

The **excretion of chloride** occurs mainly by the urine, only a small part being lost by the feces and perspiration. The normal kidneys can excrete 15 to 20 Gm. of NaCl per day. The excretion varies quantitatively with the salt income, but generally lags somewhat behind in time. The administration of salt therefore produces a temporary accumulation in the tissues. With a steady income of salt and water, equilibrium is reached, in normal man, in three or four days (Borelli and Girardi, 1915). If the supply of salt is stopped, as in fasting, the urinary and fecal Cl excretion falls to a low level within three days, the tissues retaining their normal salt content with great avidity. A small excretion (0.6 to 0.9 Gm. daily in man) continues, however, so that the tissues finally lose salt.

Diurnal Variations.—In man, the urinary chloride excretion is always greater in the forenoon than in the night, independently of meals. The midday meal has an influence, the excretion being decreased half an hour after eating, owing to the gastric excretion of HCl. This lasts an hour, and is followed by marked increase (Herrmannsdorfer, 1912).

Feces.—The fecal chloride excretion is normally insignificant, but in nephritis it may reach 3 to 5 Gm. of NaCl per day (Javal, 1903; Halpern, 1905).

Time of Excretion.—Giving 10 Gm. by mouth, the additional chloride should be excreted within twenty-four to forty-eight hours, either by diuresis or by increased salt concentration. A longer delay indicates impaired permeability of the kidney.

The observations of Vallery-Radot, 1918, may be taken as an example of the normal course: an individual on a so-called "salt-free" diet, which actually corresponded to 1.5 Gm. of NaCl per day, was excreting 2 Gm. per day. When changed to a normal diet, containing 11.5 Gm. of NaCl per day, and kept on this, he excreted, on the first day, 3 Gm.; second day, 5 Gm.; third day, 11 Gm.; fourth day to the ninth day, 11.5 Gm. daily. On changing to a salt-free diet, the reduction of the excretion followed a similar (inverted) course.

The *diuretic action* of sodium chloride is greatest if this is administered as 0.5 per cent solution; the least change of NaCl balance occurs with 0.2 per cent (J. M. Coon *et al.*, 1941; dogs).

Influence of Other Salts and Diuretics.—The excretion of Cl can be hastened by the administration of related salts (bromides, iodides, nitrates, thiocyanates). Conversely, the administration of Cl hastens the elimination of these salts, and may be useful against iodism and bromism. Diuretics have little effect; the drinking of large quantities of water reduces the percentage of Cl in the urine; the absolute quantity may be unchanged or moderately increased (Rulon and Hawk, 1911).

With dogs, theobromine and caffeine diminish the Cl, both absolute and percentage, independently of any diuretic effect (Saccone, 1911). In rabbits, these and other diuretics tend to increase the Cl excretion proportional to the diuresis (Bonnamour and Imbert, 1912). In patients with *diabetes insipidus* the daily urinary chloride is only normal, notwithstanding the enormous urine volume. The serum chloride level is also normal. Pituitrin therapy does not alter the chloride economy materially (H. Blotner, 1941).

Mechanism of Chloride Regulation.—The blood maintains its chloride concentration remarkably constant, and even the tissues undergo only temporary changes. The regulation is accomplished through the adjustment of the urinary excretion, or rather, by the degree of chloride reabsorption in the tubules. In this, the kidneys do not differentiate sharply between chloride and related ions (bromide, iodide, nitrate and thiocyanate), so that the injection of any of these increases the chloride concentration in the urine, while less related ions (sulfate, acetate, and so forth) do not have this effect (Sollmann, 1902). The mechanism by which this is controlled is not understood, but the hormone of the suprarenal cortex plays an essential part in the sodium retention. *Oral or intravenous administration* of sodium chloride releases a large amount of *pituitrin* (G. H. Chambers, 1945).

Chloride Retention.—The chloride excretion is greatly diminished in some cases of nephritis; in fevers, particularly in pneumonia (where much salt is retained in the effusion); and during the rapid development of new tissue (cancer). Salt is necessarily retained during the formation of edemas, to maintain osmotic equilibrium. Conversely, the retention of salt retains water to isotonicity, increasing the volume of extracellular fluid, and therefore disposing to effusions.

Retention in fever was first described by Redtenbacher, 1850, and has been extensively investigated, especially by Roehmann, 1889, but the subject is still controversial even as to facts. Austin and Sanderman, 1929, *f. i.*, raised doubt whether there is retention in *pneumonia*, in which it was supposed to be prominent. They attributed the low chloride excretion to the low salt content of the ordinary pneumonia diet, for with this low Cl income, the Cl balance is negative before and for several days after the crisis; and when 8 to 20 Gm. of salt were added, this was excreted quite well.

Retention in Cancer.—The diminished excretion is probably explainable by the deficient Cl income, and its need for the formation of new tissues and transudations (Gaertig, 1890; Laudenheimer, 1892).

Retention in nephritis is most likely to occur in acute glomerular nephritis (Borchardt, 1912). However, in chronic parenchymatous nephritis the ability to excrete chloride is generally impaired before the nitrogen excretion (O'Hare, 1916), and the impairment keeps step with the severity of the lesion. Chronic interstitial nephritis is not generally characterized by defective chloride excretion. The Cl excretion is increased in the early diuretic stage of uranium and cantharides nephritis; it is usually diminished with large doses of uranium or chromate. The Cl excretion bears no simple relation to the anatomic changes (Austin and Eisenbrey, 1911).

Salt Test for Nephritis.—Schlayer, 1911, kept a patient on a constant diet for several days, then added 10 Gm. of NaCl in one dose. This excess is normally excreted within twenty-four hours or at most forty-eight hours. A delay beyond this indicates diminished permeability of the kidneys to chlorides. Frothingham, 1915, classified the excess excretion within forty-eight hours of 8.5 Gm. as no retention; 4.5 Gm. as slight retention; less than 4.5 Gm. as considerable retention.

In *cardiac edema*, administration of NaCl to 75 Gm. per day causes some diuresis, with simultaneous increase of edema (Goldring, 1929).

Diabetes.—The literature contains contradictory statements as to the chloride metabolism in human diabetes (Lebensohn, 1915). The "chloride threshold" of the blood is unchanged or lowered (McLean, 1915). Sodium chloride administration to *diabetic rats* tends to restore the glucose tolerance to normal (Orten and Devlin, 1940).

Effects of Excessive Consumption of Salt.—Excess of the Na or Cl ions is ordinarily eliminated promptly; but even when they are retained, these ions *produce only slight effects*, for the amounts normally present are so large that the artificial introduction of ordinary amounts will not increase their ratio to a considerable extent. In this sense Na and Cl are the most indifferent of the ions, and their salts are used when the effects of other ions are to be tested. However, they are essential to life, and the absence of effects is due only to the fact that the variations which are introduced are relatively small.

Salt-poor diet has been used against *hypertension*, but the evidence for its usefulness is not satisfactory. Drastic reduction of sodium income by dialyzed milk appears effective in some patients, not in others. In rats with experimental renal hypertension, such dialyzed milk reduces the blood pressure and apparently prolongs life (A. Grollman *et al.*, 1945). Cl-poor diet has also been employed to enhance the retention of the bromide ion in *epilepsy* (Toulouse and Richet, 1900). Indeed the efficiency of the bromide treatment has been referred to dechloruration, but this is erroneous (see Bromides; Januschke, 1913). Restriction of chloride income greatly diminishes the polyuria of diabetes insipidus (Swann, 1939). Tables of the content of the various salts in foods are given by Albu and Neuberg, "Mineralstoffwechsel."

Limited Salt Income.—The maintenance of a certain sodium and chloride content is indispensable to the body. Animal food contains a sufficiency of this salt; herbivorous and omnivorous diets are insufficient in this respect. Under ordinary conditions, the excretion of salt keeps so nearly parallel with the salt income (Falk, 1848) that a moderate excess of salt income is practically without effect, except on the urine. A *greatly restricted salt income* (as by an excessive milk diet) *can be borne for a considerable time*, being met by a corresponding decrease of chloride excretion, so that the percentage of the salt in the blood is scarcely altered, and no general symptoms result. Dogs on a Cl-poor diet retain Cl or I more efficiently than on ordinary food (Sarvonat and Cremien, 1911). The diminished income of salt in fever seems to have no deleterious effect. Even when the excretion is further increased by liberal water diuresis, the patients show no particular craving for salt. Complete abstention from food does not produce any effects referable to the absence of salt. After a ten day fast, the total quantity of Cl in the body is reduced by only 2 per cent; and the percentage of Cl is even above the normal, because the tissues disappear more rapidly in starvation than does the Cl (Rosemann, 1912). D'Errico, 1910, found no change in the freezing point or conductivity of the blood in inanition. The inorganic metabolism in starvation was also studied by Cathcart and Fawsitt, 1907. Even *when the starvation is reinforced by active loss of chloride*, there may be no symptoms referable to salt deprivation. Hiatt, 1939, 1940, reduced the total Cl of dogs to less than half, in a week, by feeding nitrate with a chloride-poor diet. The animals were apparently normal in their actions, although there must have been considerable dehydration. Ambard, Stahl and Kuhlmann, 1934, produced severe chloride deficiency in dogs, first reducing the plasma chloride to 0.39 per cent by salt-poor food; then to 0.25 to 0.225 per cent by administering histamine to provoke gastric secretion, and evacuating this with apomorphine two or three times daily, for two weeks (Rosemann, 1912, found that the ordinary secretion of gastric hydrochloric acid stops when the chloride stock of the body has fallen by 20 per cent). This reduced level was maintained for as long as eight months. It resulted in dehydration, doubling of the alkali reserve, and diminished excretion of urea, so that the plasma concentration rose to three times the normal. This probably supplied some of the osmotic functions of the missing salt. The appetite and general conditions of the animals did not appear materially disturbed. *Chloride deficiency with normal sodium income* (by substituting $NaHCO_3$ for the NACl of a synthetic diet of rats) results in decreased appetite, increased thirst, increased heat production and diminished growth (Voris and Thacker, 1942). Hypochloremia is reported to render rabbits and cats more susceptible to convulsions (E. Spiegel and Wycis, 1939).

Excessive salt depletion results promptly in severe and fatal symptoms, owing largely to dehydration. This may occur by excessive sweating in "heat cramps"; by the loss of gastric juice in the persistent vomiting of pyloric and high intestinal obstruction; by the profuse diarrhea of cholera; and by deficiency of the suprarenal cortical hormone, and exceptionally by mere restriction of salt income. In hot climates, the capacity for work is impaired if the daily salt income is less than 15 Gm.; higher income has no advantage (H. L. Taylor, Henschel *et al.*, 1943).

Low Salt Income.—J. Forster, 1873, described severe and fatal symptoms in dogs fed on food deprived entirely of salts. But the earlier observations probably involved severe vitamin deficiencies. There have been a few similar reports recently, relating specifically to *sodium deficiency*. Himwich, Fazekas and Spiers, 1936, subjecting dogs to four to seven days of sodium deprivation, observed phenomena resembling those of adrenal deficiency, with increased total concentration of the blood and of blood urea, creatinuria, and decrease of serum chloride. Orent-Keiles *et al.*, 1937, 1940, subjected young rats for nineteen weeks to a diet containing about 0.002 per cent of Na, but adequate in other respects, and observed a fatal symptom complex, including retarded growth, ocular lesions, and disturbances of the estrus rhythms and of reproduction. There was marked retention of K, but no effect on the metabolism of Ca, Mg, P and Cl.

Prolonged emesis, as in pyloric and high intestinal obstruction, deprives the body of salt directly and by preventing absorption of food. The direct loss may be large, as the gastric juice contains about 0.5 per cent of chloride, about one and a half times the plasma concentration. The normal daily output of gastric juice, estimated as 5 liters in man, would therefore contain 25 Gm. of chloride, about three times the normal daily income. In dogs, the gastric juice amounts to 1000 to 2600 cc. per day (Dragstedt and Ellis, 1929), corresponding to 5 to 13 Gm. of Cl. However, the output would be automatically decreased by chloride deficiency. The loss of gastric juice lowers the chloride of the plasma and raises the bicarbonate, producing alkalosis (W. G. MacCallum *et al.*, 1920; Hastings *et al.*, 1921; Haden and Orr, 1923). The water content of the body and especially of the blood is diminished (dehydration) by osmotic adjustment to the lower salt content; the decreased volume and the increased viscosity of the blood diminish blood flow and oxygen supply (W. M. Marriott, 1923; Haden and Orr, 1927), resulting in shock, with death after four to eight days of complete obstruction. Intravenous injection of large quantities of sodium chloride solution may preserve life for several weeks (Hartwell and Hoguet, 1912; McIver and Gamble, 1928, references). In pyloric obstruction the alkalosis may reach the degree of severe tetany. Loss of pancreatic juice and bile, on the contrary, results in loss of alkali, and therefore in diminished plasma bicarbonate (Gamble and McIver, 1925). **Drainage of the gastric juice by a fistula** may also produce these effects (Rosemann, 1912).

Normal Cl Secretion by the Gastric Juice.—Human "appetite" juice contains 0.49 to 0.56 per cent Cl (Carlson, 1915), partly as free HCl, partly balanced by fixed bases, chiefly Na. *Salt depletion, as by drainage of the gastric juice*, markedly decreases the chloride of the gastric juice, and may suppress it entirely when the chloride stock of the body has been lowered by 20 per cent. This also produces complete anorexia (Rosemann, 1912). However, gastric juice of high acidity (about $\frac{1}{3}$ per cent HCl) may be secreted when continued total drainage of the gastric juice has lowered the blood chloride to a third (Dragstedt and Ellis, 1929).

Excessive Perspiration, Heat Cramps.—The twitchings and convulsions that occur on exposure to excessive heat, especially in confined spaces, appear to be due to the loss of salt and water by the profuse perspiration. It may be treated by intravenous injection of normal saline, and prevented by salting the drinking water, so as to maintain the urinary chloride excretion well above 3 Gm. per day (K. N. Moss, 1924; Talbott and Michelsen, 1933), adding about 2 Gm. (half a teaspoonful) of sodium chloride per quart. This is not necessary unless the daily water intake exceeds 4 liters. The *phenomena of excessive NaCl depletion*, as induced in man by a salt-poor diet, together with forced sweating and unlimited water intake, resemble those of heat stroke and Addison's disease: impairment of the sense of taste; cramps, weakness, cardiorespiratory distress on exertion; initial loss of weight; eventually increased viscosity of the blood by dehydration (McCance, 1936).

Chloride Loss by Sweat.—Moss, 1924, observed a maximal sweat loss of 5.8 pounds an hour, containing 2 to 3 Gm. of NaCl. W. M. Simpson, Kislig and Sittler, 1933, found that in a six hour hyperthermia treatment a patient may put out 3 to 5 liters of sweat, containing up to 20 or 25 Gm. of NaCl. The *chloride content of the sweat* varies with conditions and with individuals. It increases with the rate of sweating, but diminishes with acclimatization. Heat cramps are accordingly most common in the first hot spell and in men returning to work after a lay-off (D. B. Gill *et al.*, 1938). Men fully acclimatized to hard work in humid heat, producing 5 to 10 liters of sweat per day, respond to restricted salt income by reducing the salt concentration of the sweat, and so manage to preserve a salt balance with low salt income (J. W. Conn *et al.*, 1946).

Prophylaxis and Treatment of Heat Cramps.—K. N. Moss, 1924, showed that the cramps, fatigue and depression of high-temperature workers are relieved by drinking saline solution, while drinking of water may further lower the Cl concentration of the blood. Chaussin, 1933, observed that food could be salted to the extent of 10 Gm per day under ordinary conditions, but to 25 Gm. if severe labor was performed at high temperature. He also notes that the natives in hot climates use more salt than where the climate is cooler. Danielson, 1936, found that drinking of 0.6 per cent NaCl during therapeutic hyperthermia not only prevented the fall of serum Cl concentration, but actually produced a rise. It did not, however, prevent the fall of base, probably because of relatively greater loss of Cl and organic salts in the sweat. It did not materially alter the other electrolytes of the serum.

Sodium Depletion in Addison's Disease.—In experimental and clinical adrenal cortex deficiency the concentration of sodium in the plasma is markedly decreased, especially in the acute exacerbations, and this seems largely responsible for the symptoms and course; for withholding salt from the diet precipitates the attacks, and administration of salt (10 to 20 Gm. per day) improves them, as the plasma sodium is restored. The capacity of the body to retain sodium is impaired, presumably by a renal action. This appears to be specific, for there is no increase in the excretion of potassium, ammonium or acid; indeed, administration of potassium makes the symptoms worse, or precipitates an attack (R. F. Loeb and associates, 1933; H. H. Anderson and Reed, 1934). The Cl′ concentration is also decreased, more so in the corpuscles than in the plasma (Karaty *et al.*, 1939). The intestinal absorption of NaCl is decreased by adrenalectomy, that of dextrose is unimpaired (W. G. Clark, 1939).

Miscellaneous Systemic Actions of Sodium Chloride.—The ingestion of salt, without sufficient water to render it isotonic, tends to *increase the salt concentration of the body.* This affects mainly the tissues, the molecular concentration of the blood remaining practically unaltered. The increased salt concentration is counteracted by the stimulation of two mechanisms: a desire for water (*thirst*), and the elimination of highly *hypertonic urine.* If water is given freely, the salt is *diuretic.* If the water income is restricted, the poor urine flow decreases the N excretion temporarily (Degrez and Guende, 1912). *Respiratory metabolism* is increased by saline injections, especially if hypertonic (Raeder, 1915).

Saline Diuresis.—When extra salt is administered by mouth, it may increase the urine flow or the percentage of urinary chloride, or both. This probably depends on the state of the tissues more than on the kidneys. Sodium chloride diuresis does not increase the oxygen consumption of excised kidneys perfused by Starling's method (H. Gremels, 1929).

Dermatoses.—Chronic urticaria, eczema, and the like, are often aggravated by the administration of sodium chloride (to 20 Gm. per day) or other sodium salts, but not by other chlorides (Keining and Hopf, 1935).

Salt Glycosuria.—Bock and Hoffmann, 1871, observed that intravenous injection of NaCl solution into rabbits produces glycosuria. This was confirmed by Kuelz, 1872 (who also found that it does not seem to occur in dogs). The glycosuria is greater with rapid injection or higher concentrations, and may be abolished by the addition of Ca ions. The *mechanism* of the salt glycosuria is in dispute. Willenko, 1911, stated that it does not occur after section of the splanchnics and refers it to stimulation of the central nervous system. E. Hirsch, 1915, reported hyperglycemia from intravenous injection of 10 per cent NaCl. This action is central, presumably on the glycosuric center. Solutions of 2.5 per cent or more dilute, even in larger quantities, do not increase the blood sugar; nor does sodium carbonate or acetate, nor calcium chloride. Sodium sulfate also does not produce hyperglycemia (Kleimer and Meltzer, 1916). Magnesium sulfate, however, does so. Diabetic puncture and puncture of the funiculus teres in rabbits increases the urine and the percentage of chloride ("*salt puncture*"). The urinary effect is independent of the glycemia, but depends on nervous impulses carried by the splanchnics (Jungmann, 1914).

Saline Diuresis on Milk Flow.—In lactating goats, with limited water income, diuretic doses of salt or urea decrease the yield of milk and increase its fat content, presumably by diminishing the available amount of water. The nitrogen of the milk is not increased (Steenbock, 1915).

Salt Fever.—Finkelstein, 1908, and Schaps observed that the administration of salt to infants by mouth or hypodermically may produce fever. A slight rise of temperature is also observed in adults, if at least 1 liter of 0.9 per cent NaCl is injected hypodermically (Bingl, 1910), but is prevented if Ca is added, as in Ringer's solution (Bock, 1912; Burnett and Martin, 1916). The rise is accompanied by increased N metabolism and heat production (Freund and Grafe, 1911). Hypertonic salt solution (3 per cent NaCl) is much more effective (Rolly and Christjansen, 1914). A similar rise is produced by the injection of isotonic dextrose or lactose, and by indifferent particles (paraffin, colloid metals, and so on; Bock), but may have a different origin. The salt fever occurs with absolutely sterile solutions and with oral administration (Bingl; Freund, 1913). It is therefore not due to pyrogens. An apparently different type of salt fever is produced by the injection of *hypertonic solutions* of salt, glucose, and the like. This can be prevented by the administration of water and is attributed by Balcar *et al.*, 1919, to the dryness of the tissues, limiting perspiration and therefore reducing heat dissipation.

The **coronary vessels** are dilated by moderate increase of NaCl in the Locke perfusing solution (L. N. Katz and Lindner, 1939).

The **central nervous system** of frogs is inhibited if hypertonic NaCl solution is injected into the dorsal lymph sac. This "*Richet inhibition*" is abolished by section of the medulla, not by removal of the cerebrum. It is attributed to local action on the sensory nerves (Ozorio de Almeida *et al.*, 1938).

Local Actions of Salts.—Salts in isotonic or hypotonic solutions have little local action; in substance or in hypertonic solutions they act as rather mild irritants. Sodium chloride and other neutral salts, in the form of *sea baths*, produce mild but extensive stimulation of the skin, and thereby reflex tonic effects. The mechanical irritation of the dried salt crystals contributes to the result. They do not injure the epidermis. The *parasiticidal action* of fairly concentrated salt solutions is used by irrigation of the rectum against oxyuris, and of the vagina against trichomonas. They are quite effective (L. Rosenthal *et al.*, 1935).

Wright's Surgical Solutions.—A. Wright, 1917, recommended the saturation of wounds with a hypertonic saline solution, aiming to keep the surface irrigated with lymph. He employed 4 per cent of sodium chloride and 1 per cent of sodium citrate in distilled water, sterilized by boiling for half an hour. Fackenheim, 1915, had used the same principle by dressing the wound daily with granulated sugar.

Alimentary Canal.—Salt stimulates the mucosa of the alimentary canal, especially in the stomach before the salt is diluted. Hypertonic solutions produce emesis; if they reach the duodenum, they tend to evoke a "peristaltic rush" that sweeps them onward; if they remain for any time they depress peristalsis (Baur, 1926; v. Oettingen and Sollmann, 1926).

Since the salt is quickly removed by absorption, it does not cause a permanent change. The stimulation by salts may therefore be continued for a considerable time in the treatment of "atomic" *dyspepsia.* Salt may aid the digestion of otherwise difficultly digestible articles. It would be undesirable in hyperchlorhydria and especially in gastric ulcer, and the salt income should be limited in these conditions. Rosenblat, 1907, observed markedly increased secretion in the Pavlov miniature stomach, depending on the concentration; 1 per cent was indifferent; greater dilutions were slightly stimulant. Increase of gastric secretion occurs also if chloride (Na, Ca or Mg) is injected intravenously; this enjoins caution in the surgical use of saline injections, in conditions in which gastric rest is desirable (Frouin, 1922).

Laxative Action.—A teaspoonful of salt in 1 pint of water, taken before breakfast, is often laxative.

Pepsin.—W. W. Hamburger, 1915, found that neutral solutions of NaCl, even in the concentration of serum, rapidly destroy pepsin. The inhibition is complete with 2.5 per cent NaCl; scarcely perceptible with 0.25 per cent. Other inorganic salts act similarly, probably by liberation of OH ions (Hamburger and Halpern, 1915). The destruction does not occur in the presence of free acid; but once destroyed, the ferment can not be reactivated by acidulation.

The *taste of salt* is recognized by humans (and by rats) with concentrations averaging about 0.075 per cent. The difference from water is perceptible even with 0.013 per cent (C. P. Richter and MacLean, 1939).

Toxic Action.—If salt is given in large amounts and concentrated form, the irritation may lead to severe and fatal *gastro-enteritis. Poisoning by enema* was reported by Brooks, 1910. A pint of saturated solution had been injected and repeated twice at hour intervals. The symptoms were restlessness, thirst, rapid pulse, coma, fever (109° F.), frequent micturition, dyspnea. Death occurred eight hours after the first injection, preceded by convulsions and bloody discharge from the rectum.

PREPARATIONS.—***Sodium Chloride,** U.S.P. (Common Salt); NaCl; is freely sol. in water (1:2.8); nearly insol. in alc.; sol. in glyc. (1:10). Chlorides are *incompatible* with salts of silver and lead. ***Isotonic Sodium Chloride Solution,** U.S.P. (Physiological or Normal Saline Solution); contains 0.9 per cent of Sodium Chloride.

SALINE INFUSIONS AND TRANSFUSION

The injection of saline solutions, of blood serum or plasma or noncoagulable blood, and direct transfusion of blood produce similar results and are merely modifications of the same general procedure. The effects of hypodermic or intravenous injections of saline solutions on the quantity of blood, lymph and urine, and the fate of these solutions were discussed under "Salt Action." The temporary increase of plasma volume produces a moderate rise of blood pressure; this, perhaps with some direct salt action, results in increased excitability of the respiratory vagus (H. C. Jackson and Ewing, 1914) and vasomotor centers. With *normal animals*, the rise of capillary pressure is large and lasting; the rise of arterial pressure and the medullary stimulations pass off quickly, without noticeable fatigue. In *animals whose blood pressure is low*, particularly if this is due to hemorrhage, saline infusions bring the pressure toward normal, and maintain it better. Excessive injections of saline solutions may cause death from *pulmonary edema*, or from overdistention of the heart. Therapeutic injections may produce glycosuria, slight fever, and rarely albuminuria.

Factors Involved.—The effects produced by injections of sodium salts depend on the interaction of a number of factors, especially: hydremic plethora; osmotic changes; changes in the alkali reserve, by selective retention of the cation; altered ion ratio in the blood. The nature of the anion probably acts mainly by altering the permeability of the cells to sodium (Gruenwald, 1918).

Quantitative Relations.—The *volume effects* are produced by all salts the ions of which are not specifically toxic, such as most sodium salts; and by glucose, sucrose and urea. These must be used in rather large amounts, from 25 to 50 cc. of the eighth-molecular solution per kilogram of body weight. Isotonic solution of three chlorides or Locke's fluid, are somewhat better than isotonic (0.9 per cent) sodium chloride solution, but the latter suffices for all practical purposes. However, even small injections of isotonic NaCl may produce changes in blood pressure, while Ringer's solution or glucose has much less effect (Selig, 1911); so that the action is probably not wholly osmotic. Frogs' vessels are dilated by perfusion with NaCl (Hooker, 1911). Rapid massive injection of fluid under pressure of 300 mm. Hg into the cranial end of the *carotid artery* of dogs regularly results in pulmonary edema (A. A. Luisada and Sarnoff, 1944).

Vasomotor Center.—In normal animals, injections of 10 to 40 cc. per kilogram produce only slight stimulation or no change. Occasionally, when there is maintained rise of blood pressure, the vasoconstriction is marked (Pilcher and Sollmann, 1914).

"*Velocity Shock.*"—Rapid injection of practically any solution, including isotonic NaCl, may produce prompt and usually brief fall of blood pressure, together with changes in the blood, especially rapid sedimentation of the corpuscles and diminished coagulation. The mechanism is not clear, but it is probably due to alterations of the colloid state, analogous to flocculation shock. It depends on the speed of the injection, not on its bulk or temperature; but it is likely to be greater with hypertonic solutions than with isotonic or hypotonic (Hirschfeld *et al.*, 1931).

Restoration of Normal Blood Volume.—The circulation rapidly disposes of injected solutions by exchange with the tissues. As explained more fully under *General Salt Action*, the total molecular concentration, the ratio of ions, and the total volume of blood are restored to nearly normal within half an hour.

Conditions Delaying the Restoration of the Blood Volume.—In normal dogs and rabbits, the blood volume returns to normal within half an hour after the intravenous injection of warm Ringer's fluid equivalent to the total blood volume. This is delayed by morphine, and by nephritis (uranium, chromate or tartrate), but not by ligation of the kidney vessels. The restoration is not affected by the addition of 0.4 per cent sodium carbonate, either in normal or in nephritic animals (Bogert *et al.*, 1916). The restoration of the blood volume is also delayed by choline and by pilocarpine. Atropine has no effect. In peptone shock, the saline leaves the blood volume rapidly, but not completely (Underhill and Epstein, 1923). With sotonic solutions of sodium bromide, nitrate, acetate and thiocyanate the restoration occurs at about the same rate as with chloride; with sodium sulfate, the return of the old volume is less complete (A. H. Smith and Mendel, 1920).

Special Effects of Anisotonic Solutions.—*Hypotonic* solutions are somewhat more injurious and may lake the blood. *Hypertonic solutions*, by abstracting water from the tissues, produce much more violent stimulation of the central nervous system, and convulsions, always followed by depression. Small intravenous injections raise the blood pressure partly by direct stimulation of the heart (Retzlaff, 1915). With larger injections, the blood pressure shows a progressive fall, with temporary rise during the spasms. The respiration is at first quickened, but becomes slow and shallow as the blood pressure fails. The heart is quickened, feeble, and arrhythmic. In the later stages it may be slowed by stimulation of the vagus center. The temperature rises. The diuretic effect and the local irritation are also much greater. *Compensatory oliguria* follows by mobilization of posterior pituitary antidiuretic hormone (G. H. Chambers, 1945; diminution of store in rats).

Dehydration by Hypertonic Injections of Glucose or Saccharose.—In dogs, the diuresis produced by prolonged intravenous injections may diminish the body weight by 10 to 11 per cent, the plasma volume by 20 per cent, in two hours. The chloride concentration of the blood rises proportionately to the concentration of the plasma; the urea concentration of the blood also increases, although the excretion of urea is increased by the diuresis (Keith, 1924). For the use of hypertonic solutions for lowering the *cerebrospinal pressure*, see under "Salt Actions."

Toxic Doses of Different Cations.—Joseph and Meltzer, 1907, found $MgCl_2$ fatal for mammals with 0.223 Gm. per kilogram (1 cc. m/5 per kilogram per minute); Ca and K required about double, Na twenty times as much.

Balanced Solutions.—Isotonic sodium chloride solution is injurious to isolated tissues; their function requires "balanced" solutions, of the type of Ringer's or Locke's solution. This is negligible in the intact animals, because the regulating mechanisms of the body rapidly restore the normal concentration and ion ratio of the blood. Solutions of sodium chloride of 0.6 to 1 per cent may therefore be used for hypodermic, and even for intravenous, injections, although balanced solutions are somewhat more desirable, such as the "Isotonic Solution of three Chlorides," possibly with the addition of 0.1 per cent of dextrose or buffered with 0.31 per cent of sodium lactate (A. F. Hartman, 1934), or various hydrophilic colloids.

Buffering with sodium bicarbonate, 0.05 to 5 per cent, has the disadvantage of precipitating calcium carbonate, if the finished solution is heated for sterilization. This may be remedied by passing CO_2 through the sterilized solution until the *p*H of 7.35 is reached (neutrality to phenol-red); or it may be prevented by the sealing of the flask during sterilization; or the solution may be heated without the bicarbonate, which is added when the solution has cooled. Phosphate precipitates calcium on aeration, and citrate inactivates calcium temporarily. A variety of minor modifications and special formulas has been proposed, but it is not clear that these deserve preference.

PREPARATIONS OF SALINE SOLUTIONS FOR TRANSFUSION.—The U.S.P. provides three media: (1) nonsterile; (2) sterile, not for parenteral injection; (3) in water for injection for parenteral use. This last should be dispensed unless the others are specified.

Isotonic Sodium Chloride Solution, U.S.P.; 0.9 per cent. *Ringer's Solution,* U.S.P. (Isotonic Solution of Three Chlorides); contains, per cent: NaCl, 0.86; KCl, 0.03; $CaCl_2 . 2H_2O$, 0.03. *Lactated Ringer's Solution,* U.S.P.; per cent: $NaC_3H_5O_3$, 0.31; NaCl, 0.6; KCl, 0.03; $CaCl_2 . 2H_2O$, 0.02.

Colloids leave the vessels slowly, and by their osmotic or orcotic pressure they tend to retain the injected fluid, and so to diminish diuresis, lymph filtration and edemas. They therefore maintain the blood volume materially longer than do noncolloid saline injections, and so are more effective in maintaining the blood pressure in hemorrhage and shock. Gelatin, isinglass, pectin, acacia and dextran have been employed for this purpose. Their superiority, however, over ordinary saline solution is not striking, and there are some disadvantages. They tend to agglutinate the red corpuscles; and if large quantities are retained they may interfere with regeneration of the plasma proteins (W. Locke, 1944). Transfusion of blood is much more effective in serious hemorrhage; and human plasma or human albumin in other shock.

Gelatin was proposed by Hogan, 1913, but ordinary gelatin is a variable product, somewhat antigenic. It is now used as 6 per cent solution after partial degradation by *autoclaving,* which lowers its gelation temperature, and renders it nonantigenic and not liable to febrile reactions (A. Cournand *et al.,* 1944). *Isinglass* is similar. Intravenous injection of gelatin solutions produces *pseudo-agglutination* of erythrocytes, but the cells separate when they come to the small vessels and do not interfere with blood flow (R. G. Abell and Parkins, 1944). There is no immediate toxic or anaphylactoid reaction; but when the injections are repeated several times, some dogs develop serious and sometimes fatal disturbances, chiefly by *derangement of blood production* (F. S. Robscheit-Robbins *et al.,* 1944). About two-thirds of the injected gelatin *disappears from the circulation* within six hours, five-sixths in twenty-four hours. From 20 to 29 per cent of this gelatin is found in the urine (J. M. Little and Dameron, 1944). In a group of human subjects in whom a liter of 5 per cent gelatin was injected, the plasma content averaged 0.78 per cent at the end of the injection, 0.3 per cent in twenty-four hours, and considerable levels in seventy-two hours. The urinary excretion averaged 14.7 Gm. for heavy gelatin of high molecular weight, and 22.7 Gm. for light. After seventy-two hours, 80 per cent of all gelatins had been excreted (W. S. Hoffman and Kozoll, 1946).

The *diuretic effect* is considerably greater than corresponds to the injected fluid (C. E. Bridger *et al.,* 1944).

Acacia ("Gum Arabic") solution was introduced by Bayliss, 1916, 1920, adding 6 to 7 per cent to 0.9 per cent sodium chloride solution, and buffering to *p*H of 7.2. The immediate response is better and more lasting than with plain saline; but the improvement in the ultimate mortality of hemorrhage is so small that the benefit is rather doubtful, and there is some risk of serious and occasionally fatal reactions, cyanosis, dyspnea, tachycardia, pulmonary edema, and extensive necroses in the liver (Studdiford, 1937; Ohta, 1939). Some of the accidents may be due to faulty technic, but some at least are probably due to special susceptibility to the acacia itself. This produces alterations in colloidal equilibrium of the blood, which tend to sedimentation and agglutination of the corpuscles and to other anaphylactoid phenomena (Hanzlik and Karsner, 1919; A. Christie *et al.,* 1935). The susceptibility to these varies in different animals, and recognizable reactions are exceptional in man. There appears also to be considerable difference in different specimens of acacia (De Kruif, 1919). Some samples, especially pure sodium arabinate, may adsorb the calcium of the blood. Pure calcium arabinate avoids this particular danger (J. A. Maas, 1938).

The *acacia leaves the blood stream* slowly, beginning soon after injection. The progress is variable: considerable may have disappeared in six hours, most is gone in ninety-six hours, but some persists for two weeks (Emerson and Phatak, 1936). Andersch and Gibson, 1933, found 60 per cent retained in the liver, smaller amounts in the spleen, kidneys and muscle; the liver storage increases with repeated injections. Acacia was present in the liver of a dog twenty-six months after eight times the therapeutic dosage had been injected (R. E. Smalley *et al.,* 1945). The liver and spleen contained the highest concentration in a patient who died fifty days after the intravenous acacia injection (J. B. Johnson, 1945). The *plasma protein* decreases in the attempt to maintain the normal colloidal pressure, or perhaps by interference with liver function (Kendrick *et al.,* 1938; Heckel *et al.,* 1938).

Pectin is a carbohydrate derived commercially from the white peelings of citrous fruits. When autoclaved with saline at suitable *p*H, it gives a homogeneous solution of predictable viscosity and oncotic pressure (about 68 mm. Hg for the 1.5 per cent solution; S. Middleton and Wiggers, 1943). It usually requires 1000 to 1500 cc. of the 1 per cent solution intravenously to keep up the blood pressure in shock. It leaves the blood stream more rapidly than gelatin. It is nonantigenic and does not alter blood coagulability, but it hastens sedimentation and pseudo-agglutination *in vitro,* similarly to gelatin. It is partly retained in the liver, kidneys, bone marrow and spleen, and there produces foreign body reactions and cellular degeneration (W. C. Hueper, 1945), probably more injurious than with gelatin (H. Popper *et al.,* 1945; A. Cournand *et al.,* 1944).

In human subjects in whom 1 to 3 liters of 1.5 per cent pectin in saline solution was injected, the increased blood volume was maintained much longer than the pectin level, probably by mobilization of labile tissue protein. Urinary excretion of pectin started promptly, and decreased after the first day. It accounted for less than half of the injected quantity. The remainder was probably deposited in the organs (D. D. Kozoll *et al.,* 1946).

Dextran, a water-soluble, high molecular polysaccharide formed in solutions of sugar infected with a special bacterium, appears to be suitable for infusion fluids (A. Grönwall and Ingelman, 1945).

Polyvinyl alcohol of low molecular weight ("RH 623") is being tried, as 4 per cent colloidal solution, with good results in experimental shock and hemorrhages. It maintains the blood pressure about as well as does blood transfusion. It is not retained in the organs, and is reported to leave the circulation about as fast as the plasma proteins are regenerated (W. Locke, 1944; N. W. Roome *et al.*, 1944)

Particulate matter, carbon or erythrocytes, are reported to improve the flow of perfusing solutions through the capillaries by creating eddies, and to delay edema by plugging leaks in vessel walls (B. W. Zweifach, 1940).

Hemoglobin-Saline Solutions.—The addition of 5 to 7 per cent of hemoglobin to normal saline or Ringer solution endows it with about 50 per cent of the oxygen capacity of normal blood, and with sufficient oncotic pressure to prevent edema on perfusion of organs (Salaskin and Kriwsky, 1931; W. R. Amberson and Höber, 1932). The solution may be prepared by hemolyzing beef blood with water, centrifuging to remove the stromata, and adding sodium chloride to restore the molecular concentration. Dogs with half of the blood replaced by the 7 per cent hemoglobin solution are practically normal for a time, but die after five or six hours because the hemoglobin filters out of the blood vessels into the urine and feces (Amberson *et al.*, 1934; Lamson *et al.*, 1945). Clinical injection of laked blood may produce severe reactions, probably by the stroma. Aubertin, Wangermez and Sappey, 1936, claimed that a hemoglobin concentration of 14 per cent is toxic.

Administration of dextrose (glucose) may have advantages, especially in impending acidosis, and in cardiac collapse, where it acts as a nutrient (1 Gm. of glucose yields about 4 calories); in nephritis, when diminished salt permeability of the kidneys may render saline injection inadvisable; or in fever, because the oxidation of the sugar leaves the water at the disposal of the tissues. It is generally used in strongly hypertonic solutions, since these are reported less liable than the isotonic (5 per cent) solution to produce unfavorable reactions. The hypertonic solutions are also used to lower cerebrospinal pressure. Dextrose is used to protect the liver in anesthesia and hepatitis (J. P. Simonds, 1918), often with insulin; and against the hyperemesis of pregnancy (200 to 300 cc. of 25 per cent, intravenously; Titus, 1925). The injections should be graduated, so as to avoid persistent and marked hyperglycemia. Dextrose normally appears in human urine when the intravenous injection rate corresponds to 0.8 to 0.9 Gm. per Kg. per hour (Woodyatt *et al.*, 1915); and for a 70 Kg. individual this corresponds to about 63 Gm. per hour, equivalent to 252 calories or fully twice the food requirement for this time. For parenteral nutrition, at least 100 Gm. daily are necessary to prevent ketonuria. It is best given in two doses, to secure continuous utilization.

Dextrose injection in fever has distinct antipyretic action, by diluting the concentrated blood (Barbour, 1919). It is especially important against circulatory collapse, which is due largely to increased blood concentration, and especially in pulmonary edema (Underhill). Its use in *pneumonia*, especially after the third day, generally causes marked clinical improvement, with stronger and slower pulse, and apparently considerable diminution of mortality (by two-thirds, McCracken *et al.*). It probably acts partly as a food. The dosage should be at least 200 Gm. per day. Part of this may be given by mouth, so far as it is easily tolerated, the remainder by intravenous injection.

The dextrose is generally injected *intravenously*, using a very small needle, in the dosage of 50 to 75 Gm., as sterile 25 to 50 per cent solution in freshly distilled water. It is sometimes buffered with phosphate or citrate (0.25 per cent), but the reason is not clear. It is not advisable to add sodium chloride, unless there is definite salt deficiency. The rate of injection should not exceed 6 cc. of the 25 per cent solution per minute, or corresponding quantities of stronger solutions, and it is advisable to interrupt the injection for some time after each 25 Gm. of dextrose have been injected. Dextrose should not be injected *hypodermically* in large quantities, as it becomes irritating if it is not absorbed. *Intraperitoneal* injections of 5 per cent dextrose have been used in infants against dehydration (Sanford and Heitmeyer, 1928). Care must be used to avoid the neighborhood of large nerves in intravenous injections, as nerve injury has been reported (Hassin, 1938).

Dextrose, U.S.P., contains a molecule of water. *Dextrose Injection*, U.S.P., and *Dextrose Injection* in *Isotonic Solution of Sodium Chloride*, U.S.P., concentrations refer to this hydrous dextrose, which is about 10 per cent weaker than the anhydrous.

Sucrose, injected intravenously, maintains the blood volume longer than dextrose, since it is not removed as glycogen. Its hypertonic solution therefore withdraws fluid from the tissues more effectively, and it is excreted in the urine almost quantitatively in man, 70 to 80 per cent in dogs, causing considerable diuresis (N. M. Keith *et al.*, 1934). It has an advantage over sodium chloride when the kidneys do not excrete this salt effectively; but marked renal lesions from intravenous injection of hypertonic sucrose have been reported in rabbits, and also in man (W. A. D. Anderson and Bethea, 1940).

Therapeutic Uses of Saline Injections.—These are employed, intravenously or subcutaneously, to restore diminished blood volume to tide the patient over acute anemia from hemorrhage; in traumatic shock, burns and dehydration, and for parenteral alimentation.

Hypodermoclysis, subcutaneous infusion of large quantities (800 to 1200 cc.) of saline solution, should be done slowly, one-quarter to one-half hour for each half liter.

Normal saline of 0.9 per cent NaCl is usually employed, but 0.5 per cent quenches thirst more effectively.

Use in Hemorrhage.—Saline injections replace the fluid needed for effective work of the heart. The restoration of the blood pressure succeeds temporarily unless the hemorrhage has reduced the pressure to the level of shock (Pilcher and Sollmann, 1914; Downs, 1916). Short of this, the temporary benefits are often striking; but since the solution does not stay long in the vessels, the final fatality is not greatly influenced even when colloids are added. Blood plasma gives much better results, and whole blood has the advantage of replacing the blood cells as well as the fluid. *In severe but nonfatal hemorrhage,* saline infusions are more helpful for maintaining a better blood pressure and volume, and for diminishing thirst; but if the patient can take water by mouth, the result is generally quite as good as for intravenous injection of salines.

Extremes of Hemorrhage.—Dogs can usually withstand a blood loss of 2 per cent of body weight without physiological disturbance; 3 per cent produces cardiovascular reactions; 4 to 5 per cent is usually fatal (Wiggers). The greater share in the acute injury is by the loss of fluid. Richet, 1918, found that the minimum of blood compatible with survival (in dogs) is 4 per cent of the normal number of corpuscles, and 27 per cent of the normal blood mass. This survival, however, applies only to very acute experiments; the animals die in a few hours from anoxemia. Hydremic edema occurs when the plasma protein is diluted to half. Hoitink, 1935, found that the results in acutely fatal hemorrhage in dogs were no better with various balanced solutions (Ringer, Locke, Tyrode, and so forth) than with sodium chloride. In standardized hemorrhage from a large artery which gave 84 per cent mortality of untreated dogs, this was reduced to 58 per cent by saline injection, to 26 per cent by serum or citrated plasma (Ivy, Greengard *et al.*, 1943).

H. C. Wiggers and Ingraham, 1946, found the addition of sodium bicarbonate in continuous infusion fairly effective against acidosis in impending hemorrhagic shock; but lactate was not successful.

Dehydration shock, critical inadequacy of fluid and salt in the circulation, occurs as *traumatic shock* in severe wounds, especially when combined with hemorrhage. Similar dehydration shock develops in burns; and as *toxic shock* in arsenic poisoning and cholera; and in the pulmonary edema of irritant gas and pneumonia. Various mechanisms may be involved to bring about the dehydration, but the results are similar, involving loss of fluid, electrolytes and protein from the blood plasma, chiefly through increased permeability of the capillary endothelium; leading to hemo-concentration and diminished blood volumes, progressive fall of blood pressure below the critical level, soon becoming irremediable and tending to a fatal ending. Injection of saline or colloidal solutions, which are useful in hemorrhage, and in temporary cardiovascular depression as in phenol poisoning, has only limited and temporary success in replacing the fluid of dehydration shock, since the increased capillary permeability causes them to leave the circulation even more rapidly than in health. Colloidal solutions are not materially better. Frequent repetition of the injection is likely to overload the heart. When the dehydration develops more slowly, as in burns, oral administration of sodium chloride or lactate solution appears distinctly useful.

Standardized shock, as by injuring tissue with a tourniquet (F. M. Allen, 1929), has been used to compare the effects of treatment. E. Mylon *et al.*, 1943, found that intravenous injection of saline did not materially lower the mortality rate, although it doubled the time of survival. The results were not materially better when dextrose or plasma albumin or plasma globulin was added to the saline, but citrated plasma saved most of the animals. Sodium succinate also increased the recovery rate significantly. Methylene blue raised the blood pressure, but did not diminish the mortality.

Shock following unilateral occlusion of the hind limbs of dogs tends to be prevented by intravenous injection of saline solution, the Na, Cl, Ca and K ions being especially important, in decreasing order. Dextrose is relatively ineffective (L. N. Katz *et al.*, 1943; L. Friedberg and Katz, 1945; J. Meyer *et al.*, 1945).

Extensive burns produce marked hemoconcentration, so that the hemoglobin percentage may be doubled. This loss extends to electrolytes, especially sodium, as well as fluid; a third of the extracellular electrolytes may be lost in severe anhydremia. This is more serious than the loss of fluid, since fluid cannot be retained unless there is sufficient salt to keep it isotonic. In standardized burns of mice, S. M. Rosenthal, 1943, found oral or parenteral sodium chloride more effective than plasma injection. In human burns, also, serum and plasma do not prevent hemoconcentration (R. Elman and Brown, 1943). C. L. Fox, 1944, recommends sodium lactate by mouth (75 Gm. of the commercial lactate in 4 liters of water consumed freely).

Use in Uremia and Other Intoxications.—Saline solutions were extensively employed as diuretics; but it is now recognized that simple injection does not increase the elimination of the toxic substances sufficiently to be of much value.

A limited disintoxication occurs with strychnine (Hatcher and Smith, 1917; Kleiner and Meltzer, 1917). The recognition of the impermeability of the kidney to chloride in nephritis enjoins special caution. Mosenthal and Schlayer, 1913, claimed that the kidneys of experimental nephritis do not respond well to NaCl. In any case, saline injections must be used cautiously in anuria, and must not be persisted in if a moderate injection does not cause diuresis.

Plasmaphaeresis (vividialysis).—This term was introduced by Abel to designate the replacement of the plasma with saline solution. The blood is withdrawn, the corpuscles are separated and washed by centrifugation, suspended in 0.6 per cent NaCl, and reinjected. In this way much larger amounts of plasma may be withdrawn without damage, especially if the process is several times repeated. The number of red corpuscles rises at first (*i. e.*, the volume of liquid in the vessels is reduced); but ultimately they decline slowly. The plasma proteins may be reduced to a third. The urea and nonprotein nitrogen of the blood are increased. The temperature rises slightly (Abel, Rowntree and Turner, 1914; Turner, Marshall and Lamson, 1915). Amberson, Stanbury and Warweg, 1936, by using 6 per cent gum saline for replacement, reduced the plasma proteins to 0.1 or 0.2 per cent, without serious disturbance of blood pressure or production of edema. The animals recovered consciousness, regenerated the plasma proteins (in 100 hours with cats, 200 hours with dogs) and lived indefinitely. *Hepatic degeneration* (phosphorus or chloroform) delays regeneration of the blood proteins after plasmaphaeresis (Herr *et al.*, 1918).

I. Snapper, 1946, reports two clinical cases in which vividiffusion was practiced for ten to fourteen hours, removing up to 260 Gm. of urea.

● **Transfusion of blood** or plasma gives much better results than any of the substitutes; the plasma proteins remain much better in the blood stream and serve to retain fluid and salt: they tend to prevent edema; they do not overload the reticulo-endothelial cells; and they obviate the need of regenerating the plasma proteins from body stores. In hemorrhage, whole blood replaces the corpuscles, restoring the oxygen conveyance and relieving the load on hematoproteins.

Transfusion of whole blood was tried clinically in early times, with disastrous results, since foreign species were generally used. L. Panum, 1863, showed that the blood of foreign species can not be utilized for transfusion, since the corpuscles are destroyed. L. Landois, 1875, showed that foreign blood is also agglutinated, "clumped." Blood-group identity is necessary for successful injection. Worms-Mueller, 1875, investigated the acute and late effects of the transfusion of the blood of the same species, the fate of the blood, the therapeutic field, and so forth, and practically stated our modern knowledge of the subject, except some technical details (Sollmann, 1915). These observations have been confirmed by modern investigators. For instance, Weinberger, 1908, found in dogs that the water leaves the blood vessels rapidly, causing diuresis, but not nearly so great as with NaCl solution. The red corpuscles can thus be raised temporarily to over 13,000,000; but they gradually decline during the succeeding days. The specific gravity rises still more. The transferred corpuscles persist over thirty days, as judged by the agglutination reaction (Ashby, 1919). Addition of sodium bicarbonate or lactate to reinjected blood in hemorrhagic shock does not improve the chances of recovery (Ingraham and Wiggers, 1945).

Transfusion of citrated blood is discussed under Sodium Citrate. The use of *cadaver blood* is described by Yudin, 1936.

Indications for transfusion were stated by Mueller as excessive hemorrhage; carbon monoxide poisoning; and some chronic anemias, for instance, leukemia. These are practically the modern indications. Transfusion is also used to overcome the hemorrhagic tendencies of purpura and similar diseases.

Citrated human blood plasma is the best substitute for whole blood in wound shock, and has the advantage that it need not be typed and can be preserved for two or three months, or indefinitely if dried. It is better than whole blood even in hemorrhage during the stage of acute hemoconcentration; but in the later stages whole blood has the advantage of hemoglobin. The injected proteins leave the blood stream rapidly, regardless of the blood volume or concentration (W. Metcalf, 1944). Reactions are rare, and may be guarded against by negative skin tests (M. Levine and State, 1942). Pooling of the plasma inactivates the harmful substances (W. Thalheimer, 1942). Its use in *burns* was introduced by D. O. Weiner *et al.*, 1936. The dosage should be proportioned to the extent of the burn. *Bacterial contamination of plasma* may be prevented by adding 0.2 per cent of sodium sulfathiazole. This concentration is harmless when injected (M Novak, 1942).

Concentrated or dried human blood albumin has the advantage of convenience and compactness, economizing space and weight, important especially in the Navy; it does not require refrigeration for preservation, and reactions are practically absent. Plasma albumin differs from globulins in the smaller size and greater electric charge of its molecules, giving higher oncotic pressures. Their lower viscosity, owing to their more symmetrical shape, permits the injection of more concentrated solutions. Each gram of albumin holds 18 cc. of fluid in the blood stream. It is largely retained in the blood even after six hours (A. Cournand *et al.*, 1944). It is useful especially in shock and low plasma protein. The usual dose of a "unit" of 25 Gm. in 100 cc. of buffered saline solution, equivalent to 500 cc. of plasma, may be repeated in fifteen to thirty minutes. In severe dehydration it must be supplemented by fluid (C. A. Janeway, 1944). *Blood serum* is safe when properly prepared, but some serious reactions have occurred with ordinary preparation (Report, Council on Pharmacy and Chemistry, 1941, J.A.M.A., *117*).

Bovine serum "despeciated" by heating to 72° C. in the presence of formaldehyde and ammonia is reported to lose its toxicity for man, so that it may be used instead of human plasma (F. R. Edwards, 1944). Further reports may be awaited.

PREPARATIONS OF HUMAN PLASMA AND SERUM FOR TRANSFUSION.—These are obtained aseptically from eight or more humans free from transmissible disease, and pooled according to the requirements of the National Institute of Health. The average dose by vein is 500 cc.

Citrated Normal Human Plasma, U.S.P.; 10 per cent of 4 per cent sodium citrate solution is added to the fresh blood before the cells are separated by centrifugation. It may be conserved as (*a*) *Liquid plasma,* with 5 per cent of dextrose for stabilization, and with a preservative; (*b*) *Frozen plasma,* also with 5 per cent of dextrose; (*c*) *Dried plasma,* without dextrose, to be restored to the original volume by solution in 0.1 per cent citric acid.

Human Serum; coagulated for twelve to twenty-four hours, separated by centrifugation through bacteria-retaining filters, aged in refrigerator for at least twenty-eight days. Packaged *liquid* or *dried.*

◆

POTASSIUM SALTS

Potassium is widely distributed through the body and is essential to the vital functions,

but its significance is not fully understood. It acts especially on the receptive mechanism, with excitation by low and inhibition by high concentrations. The augmentory effects are usually inhibited by calcium, and potassium serves to balance the toxicity of sodium and calcium. Under suitable conditions it produces contracture of skeletal muscle and increased tonus of cardiac and smooth muscle (Fenn, 1940); but ordinarily it stimulates smooth muscle and depresses striped muscle; its effects on cardiac muscle are more complex, but generally depressant, restraining the pace-making tissue and suppressing automatic rhythmicity at lower levels of the heart; it depresses nerve fibers so that it may serve as local anesthetic; it also depresses the central nervous system. To produce these effects, however, its concentration or its ratio to the other ions must be increased considerably above the normal. With intravenous or hypodermic injections, the ion actions manifest themselves by depression of the heart and other muscles, and of the central nervous system. These effects may also be secured from toxic doses by mouth; but not by ordinary doses, since the rapid excretion prevents the accumulation of excessive potassium in the tissues, even though their absorption is somewhat more rapid than that of the sodium salt. The therapeutic use of potassium orally as cardiac and nervous depressant was a faulty deduction from the laboratory experiments. The oral administration of moderate quantities of potassium has practically only osmotic effects—diuresis, slight changes in metabolism, and so forth. The therapeutic actions of potassium salts therefore are attributable to their anions, and are practically equivalent to the corresponding sodium salts. The potassium salts perhaps produce somewhat more local irritation, and their taste is more disagreeable. They are contraindicated in renal insufficiency, since the deficient excretion could lead to the development of toxic potassium effects.

Income of Potassium.—The daily diet of man in the United States averages 3.4 Gm. (1.4 to 6.6) of potassium (H. C. Sherman, "Chemistry of Food and Nutrition," Macmillan Co., 1937). This is about a third of the income of sodium. A vegetable diet contains relatively more K. The *absorption* of potassium ingested as chloride (isotope) occurs rapidly, 90 per cent within half an hour, chiefly from the small intestines (M. Joseph *et al.*, 1939).

The distribution of potassium is in many respects converse to that of sodium. Potassium is generally more abundant in the cells, sodium in the extracellular fluids, the serum and lymph. When additional potassium is administered, it diffuses into the cells, as well as into the fluids (Bourdillon, 1937). The potassium content amounts to about a fourth per cent of the body weight, about 175 Gm. for an adult man. Of this the blood contains about 8 Gm.; the blood plasma, 0.3 Gm.; the total extracellular space, 3 Gm. About 98 per cent of the total potassium is intracellular. The mobility of K is greater than that of Na even in aqueous solution, and the difference is intensified through colloidal membranes. With cell membrane this created differences of electric potential excitability and conductivity (L. Michaelis, 1925). The body cells in general appear to be more freely permeable to K than to Na.

The *serum* of all mammals contains about 0.021 per cent of K (21 mg. per 100 cc.) and 0.33 per cent of Na. In man, the serum K ranges normally between 0.018 and 0.022 per cent, and generally the same in disease, but may rise to 0.029 per cent in nephritis and in tetany (Wilkins and Kramer, 1923; W. S. Hoffman and Jacobs, 1934; H. Unger, 1934). It is also high in deficiency of adrenal cortical secretion, and in high intestinal obstruction. In *milliequivalents* of K per liter, normal human serum ranges between 3.0 to 7.0, averaging 4.5. The corpuscles range from 72 to 102, average 82.5 (review, V. C. Myers and Muntwyler, 1940).

The potassium in *red blood corpuscles* varies greatly in different animals, generally inverse to the percentage of Na. In beef, goat and sheep, the K is about 0.055 per cent and Na 0.24 per cent; in man, pig, rabbit, horse, dog and cat, K is between 0.25 and 0.4 per cent; Na, none to 0.2 per cent. In human erythrocytes the K averages 0.423 per cent, or twenty-times its concentration in the serum (Hoffman and Jacobs, 1934). With this ratio, the sudden dissolution of a fifth of the corpuscles would liberate a fatal quantity of potassium. The potassium content of the corpuscles is reported to increase progressively in acute hemorrhage in cats, from 0.01 per cent to 0.03 per cent (J. S. Thaler, 1935). The *rate of penetration* has been studied with radioactive potassium. It requires about twenty-four hours, in life or in the test-tube, to reach equilibrium, so that the ratio of radioactive to ordinary potassium is the same in the corpuscles and in the plasma. Thirty per cent penetration requires, in life, an hour for cats, six and a half hours for man, seven and a half hours for rabbits, eight hours for guinea pigs (Mullins *et al.*, 1941).

Human cerebrospinal fluid contains 0.0126 to 0.0127 per cent, about a third less than serum (H. Unger, 1934). *Human saliva* contains 0.031 to 0.131 per cent, from one and one-half to six times as much as serum (Vladesco and Bellea, 1938).

Muscle fibers contain potassium without sodium (Fahr, 1912), but the amount is small (Hastings and Eichelberger, 1937), about 0.28 per cent of the wet mammalian muscle, 0.98 per cent of the dry weight (J. N. Cumings, 1939). The potassium in the muscle cells is all ionized (E. Bozler and Cole, 1935). The greater part of the K is not diffusible if fresh muscle is hashed cold, but it becomes diffusible if the muscle has been fatigued or heated (E. Ernst, 1932). Muscle is permeable to K ions, but not to anions (Fenn and Cobb, 1935). *When muscle is stimulated* under certain conditions it loses up to 30 per cent of its potassium. Considerable of this is taken up by the liver, and released during recovery (W. O. Fenn, 1939; review, 1936). *Nerve*, at least nonmedullated, also loses potassium during stimulation. The central nervous system and smooth muscle have not been sufficiently investigated (Fenn). *Heart muscle* loses potassium during vagus stimulation (Howell and Duke).

In the skin, the potassium and calcium are much more abundant in the epidermis than in the cuticle (Bohnstedt, 1931; Kooyeman, 1935).

After intravenous injection of potassium salts, the K leaves the plasma rapidly, the concentration returning to nearly normal in fifteen to twenty-five minutes (W. S. Wilde, 1939; Fenn, 1939), by a parabolic curve. After injection of radioactive potassium K_{42} to rats, the uptake is most rapid in the liver, heart, kidneys and lungs, slowest in skeletal muscle, brain, nerve trunks and erythrocytes. The liver attains temporarily a higher concentration (double) than the plasma; other tissues contain less than the plasma concentration. Within six hours, however, all organs have nearly the same concentration. The largest total amount by far is in the muscles (M. Joseph *et al.*, 1939; Noonan *et al.*, 1940, 1941).

Depletion of potassium, by restricted income in rats, diminished the muscle potassium by almost half, with concomitant rise of sodium, which may rise above the K. The Na in the K-deficient was intracellular, while the normal muscle Na is extracellular. The serum K was also reduced to half. The electrolytes of the liver were not materially changed (L. A. Heppel, 1939). Rats on diets extremely deficient in potassium develop necrotic changes in the heart and in the renal tubules (R. H. Follis *et al.*, 1942). *Optimal growth* of rats occurs when the diet contains five times as much Na as K (L. Redina, 1926).

Translocation of Potassium.—Potassium moves about the body rather freely, according to need. It increases in cells during their active growth, and decreases in disintegration. It goes from the cells to plasma when there is excessive loss of NaCl and water from the body, as in hemorrhage, shock, adrenalectomy. Its concentration in the blood rises during muscular activity, and falls during rest and anesthesia. It often rises and falls with the lactic acid and sugar level (review, W. O. Fenn, 1940). It rises in asphyxiation, most of the increase being from the liver, some probably from all organs, very little from muscle (W. O. Fenn, Wilde *et al.*, 1939). The liver is also the chief source of the increased blood plasma potassium in hemorrhage and shock. Traumatized muscle loses potassium and phosphate to the blood (A. P. W. Clarke and Cleghorn, 1942).

Excretion.—A considerable part of the potassium, 15 to 25 per cent, is reexcreted in the feces. The urine contains generally Na:K::2:1 to 5:3. In starvation, the ratio is reversed to 1:3. Potassium is excreted more rapidly than sodium, and is therefore more diuretic. The administration of KCl results promptly in considerable increase of the urinary excretion of both K and Na, and in increased alkalinity of the urine. These effects are more marked than with corresponding doses of NaCl (Glatzel, 1934), although the excretion of K is also hastened by the addition of Na (Biernacki, 1911). Intravenous injection of KCl or KBr, but not of K_2SO_4, renders the urine highly alkaline, with increase of bicarbonate (A. W. Winkler and Smith, 1942). A few experiments by Blumenfeldt, 1913, indicate that the excretion of administered potassium is delayed by aortic insufficiency, arteriosclerosis and interstitial nephritis. Radioactive potassium is excreted at the rate of 6 to 7 per cent per day (M. Joseph *et al.*, 1939).

Systemic Actions.—The *central nervous system* is paralyzed by excess of potassium. The reflexes suffer, then the medulla. Depression of the respiratory center leads to asphyxial convulsions. Absence or increase of K is depressant to the perfused respiratory center of the frog (Hooker, 1913). With intravenous injection, the most important effect is the cardiac paralysis.

Cardiac Actions.—Small concentrations of potassium depress and high concentrations paralyze the heart, the contractility being considerably more resistant than the rhythmicity, so that the arrested heart may contract strongly to electric stimulation. The resistance of the rhythm varies widely for the different portions of the heart, in the direction of the gradient; *i.e.*, it requires much higher concentrations to arrest the rhythm of the sinus than that of the sinus-free ventricle, which is more resistant than the sinus-free auricle. The normal plasma concentration of potassium is distinctly detrimental to the rhythm (not to the contractility) of the ventricle and auricle, and this helps to subject these to the pace-making rhythm of the nodal tissue, which is not depressed by these concentrations (Kolm and Pick, 1920; Sollmann and Chu, 1926). The tonus waves of the turtle's auricle are increased. The rhythmic depression of moderate concentrations of potassium may be more or less antagonized by calcium. Absence of potassium from the perfusion fluid abolishes the inhibitory power of the vagus on the heart (Howell, 1906).

For rabbit's heart perfused with Locke's solutions, the optimal concentration of KCl is about 0.045 per cent. Increase to 0.068 per cent (*i. e.*, one and one-half times the optimal) produces changes in the electrocardiogram which indicate depression of the intrinsic conducting system, with partial bundle-branch block. With 0.09 per cent (*i. e.*, twice the optimal concentration) these changes increase, often to ventricular fibrillation, while the auricles may continue regular. Cardiac arrest occurs at about three times the optimal concentration. All the changes are reversible when the normal K concentration is restored (McLean, Bay and Hastings, 1933). When the perfused heart of various animals has nearly stopped from potassium deficiency, and normal Ringer's solution is admitted, the heart is completely arrested for a time, before resuming rhythmic contractions ("potassium paradox," W. Libbrecht, 1921). The coronary vessels of the perfused dog heart are dilated by increasing the potassium concentration up to 1¾ of the normal, but they are constricted above this concentration (L. N. Katz and Lindner, 1939). *Pericardial application* of concentrated KCl (injected into the pericardial sac of dogs) produces electrocardiographic changes similar to those of coronary occlusion (Wiggers, 1930).

Mechanism of the Potassium Action.—The depressant action of potassium occurs in the nerve-free heart of the chick's embryo, and is therefore muscular. Howell and Duke, 1908, found that stimulation of the vagus increases the output of K in the perfused heart, especially the auricles. They attributed the vagus stoppage to the K which the stimulation of the nerve is assumed to convert from a nondiffusible into a diffusible form. Injection of potassium also liberates acetylcholine in the heart (A. B. L. Beznak, 1934), in the adrenal glands (G. Katz and Katz, 1937), and in other organs (reference: W. O. Fenn, 1940). It mobilizes adrenal epinephrine, as does also calcium chloride (G. Katz and Katz, 1937).

Replacement of potassium in Ringer's solution by other alkali metals, in perfusion of frog and turtle heart, modifies the functions: *Ammonium* increases the rate and contractility, but retards conduction; *rubidium* increases the pacemaker activity, but inhibits the contractility as well as the conduction; *lithium* has no effect on the pacemaker or contractility, but depresses conductivity slightly; *cesium* depresses all the functions (Jentgens, 1937).

Rapid intravenous injection of relatively small quantities of KCl, 2.5 to 15 cc. of isotonic solution, in dogs, produces transient hyperpnea, fall of blood pressure and slowing of the heart, by moderate stimulation of the carotid sinus, together with some direct central inhibition of the vasomotor center and stimulation of the vagus center (Winder, 1939). These effects do not occur with slow injection, and are rather slight, till the dosage exceeds a certain point, when marked cardiac disturbances develop suddenly, with decreased output, marked slowing, block, fibrillation, cardiac arrest, usually before the respiration stops (Mathison, 1911). The *ventricular fibrillation* may result either from increased excitability or by local increase of the refractory period (Wiggers, 1930). These recover spontaneously and promptly, unless the circulation was arrested by the fibrillation. *Slow continuous injections* into dogs or cats produce only minor changes of blood pressure until the final cardiac failure occurs (H. B. Hoff *et al.*, 1939). Larger doses depress the heart muscle directly, even when the vagi are divided. Fatal doses produce ventricular and eventually auricular fibrillation (Hering, 1915). With plasma concentration of 12 to 20 m. eq. per liter, the intravenous toxicity of KCl is diminished by the addition of $CaCl_2$ (A. Winkler *et al.*, 1939) and of NaCl (Amberg and Helmholz, 1916). Skeletal muscle continues to contract after the cardiac muscle is paralyzed. *Arterial injection* causes immediate rise of blood pressure, by stimulation of the vasomotor center, and of the vessels directly (it occurs even when the central nervous system is destroyed, Mathison, 1911).

Ventricular fibrillation is arrested by adequate doses of potassium, and a regular rhythm of the heart may then be started by suitable stimulation. This may be effective, for instance, in electrocution (Wiggers, 1939). In dogs, intravascular injection of 50 mg. of KCl, as 5 per cent solution, per Kg. of body weight, to arrest the fibrillation, then 5 per cent $CaCl_2$, 1 cc. per Kg., with cardiac massage, was successful in less than half of the animals. Better results were obtained by arresting the fibrillation by alternating current, according to Hooker *et al.*, 1933.

Skeletal muscle of frogs is weakened by excess of potassium, the height of contraction is diminished, the latent period lengthened and excitability and conductivity decreased (Fahr, 1910). Veratrine contracture is abolished, but on the other hand, hypertonic KCl produces contracture by itself (F. Buchthal and Lindhard, 1939). In mammals, intra-arterial injection of KCl temporarily increases the response to stimulation, also after curarization, similar to stimulation of the sympathetic nerve supply (A. M. Baetjer, 1935; T. P. Feng, Lee *et al.*, 1938). Somewhat larger doses depress the neuromuscular transmission and then block it, with marked contracture. The response to direct stimulation is not impaired (S. M. Walker, 1947). Intravenous injection counteracts the decreased tension after repeated stimulation, perhaps by replacing the potassium lost in contraction (H. E. Hoff *et al.*, 1941).

Deficiency of potassium has no effect upon the contraction range of a toad gastrocnemius muscle; or upon its ability to pass into a state of tetanus; but the ability of the muscle to maintain a condition of tonus is impaired (Neuschloz, 1923). Potassium is essential for the transfer of PO_4 from phosphopyruvate and phosphoglycerate to creatine in homogenized muscle. It is not replaceable by Na, and is inhibited by Ca (Boyer *et al.*, 1942).

Sensitization of excised muscle to potassium is produced by veratrine, aconitine and delphinine; by thiocyanate, thiosulfate and colchicine; by chloropicrin and bromopicrin; and by guanidine. Susceptibility to acetylcholine is not raised materially. The thiocyanate acts chiefly at the level of the muscle cell; the guanidine at the myoneural junction; the veratrine on both (G. Coppée, 1942).

Clinical myasthenia is reported to be improved by the oral administration of large doses of KCl (Laurent and Walther, 1935), and the symptoms of *myotonia* increased, similarly to prostigmine (Russel and Stedman, 1936). The attacks of *familial periodic paralysis* are reported to be associated with marked fall of the serum K, and to be improved by administration of potassium salts. The paralysis is central and does not occur in normal persons when their serum potassium is reduced to the same level (Allott and McArdle, 1938; Pudenz *et al.*, 1938; G. D. Gammon, Austin *et al.*, 1939; references, W. O. Fenn, 1940).

Deficiency of adrenal cortex function, experimental and in the crises of Addison's disease, is associated with high concentration of K in the plasma, as well as low concentration of Na, and both conditions are remedied by the administration of adrenal cortex. As intraperitoneal injection of large doses of KCl produce phenomena similar to those of adrenal deficiency, it is advisable to restrict the K income of such patients (Zwemer and Truszkowski, 1936).

Smooth Muscle.—The tonus and contractions of the intestines, uterus, bronchi and arterioles are stimulated by excess of potassium (Mathison, 1912). However, the vessels of frogs are dilated by perfusion with potassium (Hooker, 1911).

Amebae immersed in isomolecular KCl solution (0.025 M.) show reversible inhibition of locomotion and marked increase of protoplasmic viscosity. Both effects are produced by acidifying the solution to *p*H4 (Corson, 1944).

Ciliary motion is but little affected by potassium (Ishikawa and Ohzono, 1931).

Nerve.—Excess of potassium depresses the oxygen consumption of nerve (T. H. Chang *et al.*, 1935). Injection of K suspends the conductivity of nerve and potentiates the anesthetic effect of cocaine. Na, MH_4 and Mg do not have this effect (Zorn, 1913). Injury and the local application of lipolytic anesthetics increase the concentration of K ions in medullated nerve fibers. This may play a part in the anesthetic effect (Menten, 1912). Under clinical conditions the local anesthetic action of potassium salts is almost insignificant, since the potassium is rapidly absorbed or "neutralized" by other ions in the tissues (Sollmann, 1917). However, 1 per cent potassium chloride may be used in place of normal saline for the dilution of the more active anesthetics.

The *excitability of the sympathetic cervical ganglion* to stimulation of the preganglionic nerve or by acetylcholine is increased by potassium (Feldberg and Vertiainen, 1934).

Potassium Therapy of Allergic Disorders.—B. Bloom, 1938, reported prompt and striking improvement, often within a few minutes, in hay fever patients from oral administration of potassium chloride, 0.3 to 0.65 Gm., 5 to 10 grains, three times daily. Most other clinicians have not obtained a definite response (H. Miller and Piness, 1940; G. F. Harsh and Donovan, 1940; S. S. Rubin *et al.*, 1940).

Location of Potassium Action.—Excised tissues respond to potassium excess, deficiency and restoration much more rapidly than the ion can pass into or out of the muscle cells (Urano, Fabr). It must therefore act on the cell surface or membrane. It has been suggested that the high migration speed of the K ions would upset the surface potential.

The **effects of oral administration** of an ordinary dose of potassium salts are chiefly, if not exclusively, those of the anions, since the potassium is so readily excreted that its concentration in the blood or tissues does not rise materially unless very large doses are given, or if the excretion is seriously checked by renal disease.

In man, oral ingestion of 12 Gm. of KCl is generally not toxic, although the plasma potassium is raised by about two-thirds in two hours (M. Norn, 1929); 0.1 Gm. of potassium salt per Kg. of body weight generally does not produce demonstrable harmful effects; but in some individuals 0.08 Gm. per Kg. is harmful to the kidneys, reducing the inulin and urea clearance. The electrocardiogram frequently shows increased T wave even with 35 mg. per Kg., also changes of renal function (N. M. Keith and Osterberg, 1946). Paresthesias sometimes occur if the serum level reaches 30 mg. per cent. Rats suffered no harmful effects when the potassium of the diet was four times that of the sodium (H. G. Miller, 1923). Rapid intravenous injection of 1 per cent solution may cause intense pain along the vein; this does not occur with slow injection (N. M. Keith *et al.*, 1941). The intravenous toxicity of KCl is diminished by simultaneous injection of calcium salts (Winkler, Hoff and Smith, 1939) or of hypertonic sodium chloride or dextrose (G. Amberg and Helmholz, 1918). Administration of *desoxycorticosterone* or of *thyroid* increased the tolerance of rats for intraperitoneal injection of potassium chloride (B. E. Lowenstein and Zwemer, 1943).

Potassium Poisoning in Nephritis.—The administration of 5 to 10 Gm. of KCl (diluted) usually produces no symptoms, even when the permeability to NaCl is impaired, as in chronic nephritis, and it is doubtful whether oral administration of potassium salts can lead to the accumulation of a fatal concentration unless there is complete anuria. Occasionally a nephritic patient may develop severe potassium poisoning, as in a case described by Smillie, 1915. The symptoms started after seven hours and reached their maximum in twenty-one hours. They consisted in cyanosis, weak pulse and vomiting. Cardiac arrest preceded by progressive electrocardiogram changes characteristic of potassium poisoning were recorded in several deaths of uremic patients with fatal serum potassium concentration (J. F. Marchand and Finch, 1944; N. M. Keith *et al.*, 1944). *Removal of the kidneys or ligation of the ureter* in dogs raises the serum potassium progressively, with electrocardiogram changes characteristic of potassium until cardiac arrest occurs, chiefly by potassium accumulation (H. E. Hoff, Smith and Winkler, 1941). Direct introduction of potassium salts into the stomach or duodenum after ligation of the ureters hastens death (A. W. Winkler *et al.*, 1941).

Potassium in the Toxicity of Urine.—Intravenous injection of urine produces a variety of effects, differing qualitatively as well as quantitatively according to the origin of the urine, and the animal into which it is injected. (Hatcher and Smith, 1916, found that intravenous injection of urine is not toxic for cats.) Various theories and methods of diagnosis have been built around the differences of toxicity, but too many factors are involved. A part of the effects is due to potassium, but unidentified organic constituents also play an important part (Kuizumi). These are apparently formed largely in the kidney, for death occurs much earlier if the urine is continuously reinjected (by implanting a ureter in a vein) than if the kidneys are excised (Galehr and Tadashi, 1927).

B. Zondek and Black, 1946, report that dialyzed human urine, adjusted to isotonic, is not toxic for rabbits and rats by intravenous injection, nor for the frog heart.

Potassium-deficient diet causes the death of rats in about twenty-three days, preceded by loss of weight, shortening of hair, cyanosis, cardiac slowing and irregularities, abdominal distention, lethargy and coma. Marked ascites is common, and the viscera, especially the heart muscle and kidneys, show degenerative changes (Schrader, Prickett and Salmon, 1937; Keiles and McCollum, 1941). The minimal requirement appears to be 0.17 per cent of the diet (Kornberg and Endicott, 1946).

Administration of Potassium.—Potassium salts are used chiefly for the anion, but sodium salts generally deserve preference. The taste of potassium is less salty but more disagreeable. It is more easily excreted, and is therefore less liable to cause salt edema. If large quantities of salts are administered over long periods, as with bromide in epilepsy, it would be theoretically desirable to balance the sodium with potassium, perhaps in the serum ratio of 15 to 1. Practically, however, this does not appear to be material. If potassium is used for its own sake (as in myasthenia), it is administered as *Potassium Chloride,* U.S.P., which is readily soluble in water, but which should be diluted to at least 1 per cent. The dosage is stated as 1 to 2 Gm. (15 to 30 grains). *It must not be confused with the toxic chlorate. Potassium Chloride Tablets,* U.S.P.; usual sizes 0.3 and 0.5 Gm.

LITHIUM SALTS

Lithium urate is relatively soluble. By a misinterpretation of this chemical fact, the lithium salts were introduced as solvents for uric acid, and hence as remedies against gout, rheumatic conditions, and the like (lithium carbonate, 0.12 to 0.3 Gm.; citrate, 0.3 to 0.6 Gm.; both soluble in water). Since the soluble urate can not be formed in the presence of sodium or potassium ions, it can not exist in the body or in the urine. The uses of lithium salts therefore have no rational foundation, and larger doses are somewhat dangerous.

The actions of lithium resemble those of potassium, but it is less toxic to the heart, and causes a vagus stimulation. These effects are seen only on intravenous injection. It may be used to replace Na in frog heart perfusion, requiring only a slight increase of K and some decrease of Ca (Dulière, 1927). An important difference from potassium consists in a *specific gastro-enteritis* which is produced even when the salts are given subcutaneously, or if the administration of moderate doses is continued for some time (1 Gm. of the carbonate in man). The lithium is largely excreted by this channel. It is also excreted by the kidneys, but does not cause nephritis (Krumhoff, 1884; Good, 1902), and also in the milk (Koldewijn, 1910). *Acute poisoning from larger doses* in man (four doses of 2 Gm. of LiCl) is described by Cleveland, 1913. There were no gastro-intestinal symptoms; but marked muscular and general prostration; vertigo, and eye and ear symptoms resembling those of cinchonism.

Action on Urates.—Lipowitz, 1841, found that lithium carbonate is a better solvent for uric acid (about four times) than sodium carbonate. He suggested its therapeutic use, and this was introduced by Ure, 1844, and Binswanger, 1847. Garrod, 1861, found that gouty tophi were dissolved in lithium solution. The solvent action, however, occurs only when strong solutions of lithium carbonate act on uric acid. In the presence of NH_4, Na or K, the less soluble urates of these cations are formed. The solution can not therefore occur under the conditions of the body or urine. Lithium salts have diuretic actions (Husemann), but no greater than the Na salts. The slight superiority of lithium could exist only with very large doses, and these are unsafe (Haskins, 1916). The popular "Lithia waters" have been shown to be practically devoid of lithium. The best contain only 0.01 to 0.02 per cent. "Buffalo Lithia Water" contains only a fifth as much lithium as Potomac River water; 200,000 gallons would be needed to supply the ordinary therapeutic dose of lithium.

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CESIUM AND RUBIDIUM

These also resemble potassium and may replace it in the excised frog heart (Zwaardemaker, 1918). Potassium deficiency in the diet of rats may be largely replaced by cesium and more effectively by rubidium. These prevent the myocardial necrosis and the damage to the renal tubular epithelium. Convulsive seizures were noted (R H. Follis, 1943).

Cesium exists normally in the retinal layers of the eyes of pigs, sheep and oxen (G. H. Scott and Canaga, 1939). Its excretion was studied by C. F. Graham and Wright, 1933.

Rubidium iodide and bromide were introduced into therapeutics, with the improbable claim that they produce less iodism and bromism. The doses are the same as those of the potassium salts.

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AMMONIUM SALTS

Ammonium is formed in normal metabolism as a precursor to urea. Through this it plays an important role in neutrality regulation. It produces the "salt actions" of indifferent salts, and penetrates readily into cells, as ion and especially as ammonia gas, which is formed from it in alkaline solutions. Its actions per se are not pronounced or important. Ammonium salts are used chiefly as carriers of acid actions (chloride) or alkali actions (hydroxide or carbonate locally, acetate systemically).

Absorption and Excretion.—Ammonium salts are absorbed from the digestive tract, and what is not converted into urea is excreted by the urine, probably more readily than other cathions. Absorption and excretion of *gaseous ammonia* by the lungs is doubtful, or slight at most. It was denied by Magnus, 1902, and Brucini, 1907. Hoeber, 1912, and McGuigan, 1913, claimed that the inhalation increases the percentage of ammonium in the blood. However, this insignificant absorption occurs from the trachea and bronchi, and also from injured alveoli (Magnus *et al.*, 1914). W. Coleman, 1916, stated that traces of ammonium can be discerned in the *sputum* (not in the saliva) twelve hours after discontinuing small doses of the salts.

Penetration of Cells.—The ammonium ion, like other cations, diffuses very little into cells, including erythrocytes. Ammonia, NH_3, which is formed by the hydrolysis of ammonium salts of weak acids, enters cells readily. In erythrocytes, this results in *hemolysis* (Jacobs and Parpart, 1938).

Disintoxication of Ammonium.—Ammonium is partly excreted as such by the urine; but the greater proportion is rapidly converted into urea by splitting off two molecules of water. This liberates the acid ion with which the NH_4 was combined, and this seizes upon the free fixed alkali of the body, and so diminishes the alkali stock of the tissues. In this way any excess of ammonium introduced into the body is soon eliminated, or at least ceases to act as ammonium.

There is similarly a fairly definite relation between the ammonium excretion, the reaction of the urine and acidosis conditions (Hasselbalch, 1916). Ingested ammonium disappears rapidly from the circulation, even if the kidneys are ligated (Jacobson, 1914). The conversion of ammonium carbonate into urea is practically complete in all mammals. Ammonium chloride is destroyed more efficiently by herbivorous animals than by carnivores or man. In man, after the administration of 5 Gm. of ammonium chloride, 52.5 per cent was recovered from the urine in two days (Wolf and Osterberg, 1912).

Ammonium in Metabolism.—Arterial blood contains normally about 1.5 mg. of NH_4 per 100 cc. Portal blood contains from 3.5 to 8.5 mg. (Carlson and Jacobson, 1910). Folin and Denis, 1912, believed that the excess in the portal blood comes mainly from bacterial changes in the large intestines. The ammonium is probably a normal forerunner of urea. This is formed from ammonium carbamate by the subtraction of H_2O. *The source of the endogenous ammonium* of the urine is chiefly glutamine; other amino acids may add a minor quantity. This conversion is increased by acid, decreased by alkali. It diminishes the amount of urea that can be formed. *Urea* is not transformed into ammonium, but is excreted as such (D. D. Van Slyke, Phillips *et al.*, 1943).

Function of Ammonium in Neutrality Regulation.—The transformation of ammonium into urea is utilized for the control of the reaction of the body: when there is excessive formation of acid (acidosis), the transformation is less complete, the acid being neutralized by the ammonium and excreted in the urine. If alkalis are administered, the ammonium is displaced from its salts, and converted more completely, so that none may appear in the urine (Janney, 1912). The ammonium-urea relation of the urine is thus an index of the acid production or alkali income. The ammonium excretion is high in diabetes (Boussignault, 1850), where a tendency to acidosis is present.

Place of Urea Formation.—The transformation of ammonium into urea occurs in perfused *liver* (v. Schroeder, 1892; Fiske and Karsner, 1913); the urea may also be considerably higher in the hepatic than in the portal blood (Van Slyke, Cullen and McLean, 1915). No urea is formed in dogs after excision of the liver, so that this appears to be the sole place of urea formation (J. L. Bollman and Mann, 1933), although it was believed that all organs participate, especially in its formation from amino acids (Folin, 1914; S. Bliss, 1929). However, the *ammonium formation* for protection against acidosis appears to occur exclusively in the kidneys (S. R. Benedict and Nash, 1926).

Utilization of Ammonium Nitrogen.—Grafe and Schupfer, 1912, claimed that ammonium may replace the protein food. This was confirmed by Knoop, 1913, Grafe, 1914, and others. It does not prove that ammonium is converted into tissue nitrogen. It is more probable that it is utilized by the intestinal bacteria, which are then digested and their nitrogen absorbed. Accordingly, Henriques and Anderson, 1914, found no retention of nitrogen after the intravenous injection of ammonium or urea. Taylor and Ringer, 1913, observed considerable N retention after oral administration of ammonium carbonate, but the associated changes in metabolism indicate that the retention is due to a toxic action of the ammonium, rather than to its utilization (Underhill and Goldschmidt, 1913).

The ammonium content of the blood has not been found increased in uremia or in acute yellow atrophy of the liver. An increase of 50 per cent above the normal has been reported after complete excision of the thyroids and parathyroids (MacCallum and Voegtlin, 1909; Berkeley and Beebe, 1909); and the ammonium production is increased (Underhill and Saiki, 1908), or its destruction diminished (Carlson and Jacobson, 1910). A similar increase was reported in clinical tetany (Musser and Goodman, 1909). However, Carlson and Jacobson, 1911, showed that the increase of ammonium is not constant and falls within the variation of normal animals, so that even these conditions can not be classed as ammonium intoxications. McNeil and Levy, 1917, concluded that increase of blood ammonium above 1 mg. per 100 cc. which occurs in various diseases, is not connected with acidosis, but rather with hepatic disturbance, especially of the acute functional type.

Ammonium chloride acidosis has a twofold basis: the direct acidity of the salt of a strong acid and a weak base; and the conversion of part of the ammonium into urea, leaving an excess of chloride anions, which neutralize a corresponding amount of the alkali reserve of the body (Haldane, 1920). The direct acidity is responsible chiefly for the immediate effects on the circulation and respiration when ammonium chloride is injected intravenously. The acidification of the urine is due entirely to the second mechanism, since the ammonium concentration of the urine is insignificant. The change in the acid-base equilibrium is also chiefly due to the second mechanism, for it becomes marked only when the ammonium is converted into urea, and is still apparent after six weeks (as low oxygen and carbon dioxide content of the blood), when the ammonium has completely disappeared (Haldane, Linder *et al.*, 1928).

Therapeutic use is made of this acidosis to acidify the urine so as to render it bactericidal and as an aid to hexamethylenamine and to mandelic acid; to combat alkalosis; to mobilize and remove lead in chronic lead poisoning; to diminish convulsions, as those of epilepsy or camphor, the rationale being obscure; and to reinforce the action of organic mercurial diuretics. The *dosage* for these purposes is 1 to 2 Gm., 15 to 30 grains, four times daily, freely diluted with water, or as enteric capsules. Excessive acidosis should be avoided.

Diuresis may be produced by ammonium chloride alone, but is not practical, as it requires very large doses, at least 15 Gm., or even 40 Gm. per day (N. Keith, 1931), which tend to cause too much acidosis and disturbance of the salt equilibrium. *Ammonium acetate solution,* which tends to render the urine alkaline, has been employed as a mild diaphoretic and diuretic in fevers, but is presumably useless.

Intravenous injection of ammonium chloride produces immediate increase of respiration, fall of blood pressure and slowing of the heart, partly the results of the acid reaction of the salt; but injection of ammonium carbonate and hydroxide produces similar respiratory stimulation (Brassfield *et al.*, 1946).

With large doses, Marfori, 1893, described prompt tremors and twitchings, progressing to tetany, violent convulsions and opisthotonos; irregular respiration; salivation and emesis; somnolence and lassitude. If the injection is not promptly fatal, the functions recover rapidly (Meneguizzi, 1912). The *respiratory activity* produced by intravenous injection of ammonium chloride has been investigated by C. R. Brassfield *et al.*, 1945. *Acetoacetic acid production* from pyruvic acid in the liver is increased by ammonium chloride, *in vivo* (Annau) and in liver sections (Edson, 1935).

A *curare-like effect* on skeletal muscle is demonstrable with ammonium, but it is much weaker than with the organic ammonium bases. This is presumably the explanation of the relief of toxin tetanus which was reported by Dixon and Ranson, 1930, for large doses of ammonium chloride in rats.

Plant Tumors.—The injection of ammonium salts and a number of other substances produce tumor-like cell proliferations in plants (E. F. Smith, 1917). They are probably due to removal of growth-restraining factors

Ammonia as Stimulant.—Ammonium carbonate and hydroxide, which liberate gaseous ammonia, are used for reflex stimulation by inhalation (especially as ammonium carbonate, "smelling salts," "sal volatile"), or by oral administration of "aromatic spirit of ammonia." This is also used as alkaline carminative in dyspepsia. It contains 4 per cent of ammonium carbonate, 0.2 per cent of ammonium hydroxide, with aromatic oils and alcohol, which renders the ammonia less irritant (Robert Boyle), by reacting with it to form aldehydes. Half a teaspoonful to a teaspoonful is taken in water. The freshly made spiritus turns milky, but the aged forms a clear solution with water. *Inhalation of ammonia vapor* stimulates the medullary centers through the sensory trigeminal endings, producing momentary standstill, then increase of respiration; stimulation of the vasomotor center (rise of blood pressure); and vagus slowing of the pulse (in rabbits, vagus standstill). It is used for stimulating the medulla reflexly in headache, fainting, collapse, excessive anesthesia, and so on. Care must be used so that the unconscious patient is not made to inhale too concentrated a vapor, which may cause laryngitis, bronchitis and pneumonia.

Applied to the skin, ammonia produces rubefaction, and if concentrated and confined, vesication, usually without corrosion. It is used in combination with oil (ammonia liniment) for counterirritation in rheumatism, and so forth. Ammonia also is applied to insect bites.

Expectorant Action.—Ammonium chloride is said to make the sputum subjectively "looser," easier to raise, and perhaps more abundant. The increased secretion of mucus and saliva is mainly a reflex from the local irritant action, although there may be some direct central stimulation (V. E. Henderson, 1910). The liquefaction of the mucus may be due partly to the excretion of the alkaline ammonium carbonate by the saliva. This excretion, however, is small, since most of the ammonium is destroyed in the body. Ammonium chloride is also said to have a primary astringent effect on the mucous membrane. Ammonium chloride is used in acute and chronic bronchitis in the dose of 0.3 Gm., 5 grains, repeated as needed; either as troches (0.1 Gm., 1½ grain) or in solution. Its disagreeable taste is less noticeable in acid mixtures (*syrup of citric acid*).

The *expectorant actions of ammonium carbonate* are more definite, as its alkalinity liquefies the mucus, and the irritation and nausea are more marked. The saliva, however, is rendered more acid (Brassfield *et al.*, 1946). It is used, 0.1 to 0.3 Gm. in solution, when the mucus is thick and purulent. Its taste is disagreeable. Syrups of Glycyrrhiza, Wild Cherry and Tolu are used as flavors, not very successfully. It is *incompatible* with Syrups of Citric Acid or Orange.

Toxicology.—The neutral ammonium salts may cause gastritis. This would be treated by dilution and evacuation. Ammonia and the carbonate produce more violent irritation, and also inflammation of the respiratory passages. The mortality of ammonia poisoning is therefore high. If the patient recovers from the acute effects, pneumonia may set in; or the hoarseness or aphonia may last for months. The *treatment* consists in artificial respiration, weak acids and oils.

Preparations.—***Ammonium Chloride,** U.S.P. (Sal. Ammoniac; Salmiac; Muriate of Ammonia), NH_4Cl, is a white crystalline, odorless powder, of cooling saline taste. Freely sol. in water (1:2.6); sol. in alc. (1:100); freely sol. in glyc. (1:8). Neutral or slightly acid to litmus. *Incompatible* with alkaline hydroxides or carbonates (liberation of ammonia). Dose, as expectorant, 0.3 Gm., 5 grains, every three or four hours; as diuretic, 3 to 6 Gm. daily. *Ammonium Chloride Capsules,* U.S.P.; usual sizes, 0.3 and 0.5 Gm. *Ammonium Acetate Solution,* U.S.P. (Spirit of Mindererus), is 7 per cent $NH_4C_2H_3O_2$, with small amounts of acetic and carbonic acids. Should be slightly acid. Must be recently prepared. Dose, 15 cc., 4 drachms.

***Ammonium Carbonate,** U.S.P. (Sal Volatile, Hartshorn, Bakers' Ammonia), is a mixture of varying proportions of acid ammonium carbonate (NH_4HCO_3) and ammonium carbamate ($NH_4NH_2CO_2$). For medicinal purposes, only the translucent pieces are used. On exposure to air, it becomes a powder, losing NH_3 and CO_2; and changing to ammonium bicarbonate, NH_4HCO_3. White, hard, translucent, striated masses; strong odor of ammonia, without empyreuma; sharp, saline taste. It dissolves slowly in four parts of water, the carbamate changing to normal ammonium carbonate. It is decomposed by hot water. Alcohol dissolves the carbamate and leaves the carbonate. Incompatible with acids and the salts of most metals and alkaloids. Dose, 0.3 Gm., 5 grains. ***Aromatic Spirit of Ammonia,** U.S.P. (Spiritus Ammoniae Aromaticus; Aromatic Ammonia), is a solution of ammonium carbonate (4 per cent), ammonia water (2 per cent) and aromatic oils (1.2 per cent) in 70 per cent alcohol. A nearly colorless liquid when freshly prepared, but gradually acquires a yellowish color. Dose, 1 to 4 cc., 15 to 60 minims, in a glass of water.

Diluted Solution of Ammonia, U.S.P. (Ammonia Water), contains about 9.3 Gm. of NH_3 in 100 cc. It loses strength on standing. Colorless liquid of pungent ammonia odor and caustic soapy taste. Freely miscible with water and alc. Incompatible with most metals and alkaloids. Dose, 1 cc., 15 minims, largely diluted. *Strong Solution of Ammonia,* U.S.P., contains 28 per cent ammonia. *Ammonia Liniment* (Household Liniment) is a mixture of 1 part ammonia water, 1 part almond oil and 2 parts olive oil.

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EXPECTORANTS

This term, literally "out of the chest," has been extended to all remedies that quiet cough. This comprises the following approaches: *Anodyne expectorants,* especially opiates, which dull the appreciation of the cough reflex. They give the most effective symptomatic relief, and may be justified to secure rest; but they do not remove the pathologic condition. *Local anesthetics,* such as orthoform lozenges, are no more desirable and are less effective. *Demulcent expectorants,* acacia, licorice, sugar or syrup, glycerin diminish the cough sensation by protecting the inflamed mucosa of the pharynx; and are therefore directly beneficial, especially against "rawness" or "nervous tickling." *Astringents* (lozenges of tannin or catechu) furnish a protective coating and contract the inflamed vessels, but their action does not extend below the larynx. *Nauseants,* by increasing the secretion of mucus, furnish the protection of demulcents, but extend also into the bronchioles. They liquefy the mucus, and therefore render expectoration easier, as has been confirmed by roentgenoscopy (Gordonoff, 1938; the ciliary movement contributes little to the transport of viscid mucus; Gordonoff and Mauderli, 1936). The nauseants which act centrally (ipecac and antimony) are called *sedative expectorants,* because they depress the patient. Those which act by local irritation (senega, squill) are termed *stimulant expectorants,* because they stimulate the mucosae directly.

Liquefying expectorants promote expectoration by decreasing the viscosity of the mucus. *Alkaline expectorants,* sodium bicarbonate or ammonium carbonate, may be used for this purpose above the larynx, as lozenges; their action may be extended into the larger bronchi by spraying. *Saline expectorants,* ammonium chloride and potassium iodide, extend the action to the entire bronchial tree. *Aromatic expectorants,* terpene hydrate, various volatile oils, tar, are used especially in chronic bronchitis, to promote a reaction toward healing; they are also employed if the secretion is thin and abundant.

E. M. Boyd, 1946, reports that the *output of fluid from the respiratory tract* is increased by acid ammonium salts, guaiacol, ipecac and iodides when absorbed; and by syrups when given by mouth, but not by stomach tube.

The great number of expectorants is not generally needed. The following suffice to meet conditions in the most effective manner: *Against dry congestion:* Syrup Ipecac, 1 cc., or Tartar Emetic, 5 mg. *Against thick secretion:* Ammon. Chloride, 0.3 Gm.; KI, 0.25

Gm. *Against excessive thin secretion:* Terpene Hydrate, 0.15 Gm. in capsules. *Against irritation:* Codeine, 5 mg.; alkaline gargles.

Cough Mixtures.—These polypharmacal preparations usually contain morphine and therefore give relief; but since they can not meet the special indications of the different stages, they should be avoided. They are illustrated by the "Brown Mixture," whose activity depends on antimony and opium; and by *Compound Syrup of White Pine*, N.F.

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UREA

Urea, $CO(NH_2)_2$, produces the physical "salt actions," as it is easily absorbed and diffused, and its toxicity is low.

Fate and Excretion.—Urea is not utilized in nutrition (Henriquez and Anderson, 1914). When additional urea is administered, it is excreted promptly and completely, mainly by the kidneys. The excretion is impaired in chronic interstitial nephritis (v. Monakow), but not in chronic parenchymatous nephritis, so that urea has been recommended as a diuretic in the latter condition (McLean). The sweat also excretes a small amount of urea (0.21 per cent, Kovesi). The urea content of the milk is not increased by urea administration (Steenbock, 1915).

Diuretic Action.—As urea is a nonthreshold substance, it is effective as a diuretic and may be used for this purpose provided that the glomerular function is not impaired, so that it does not raise the blood urea nitrogen materially. Urea inhibits water absorption in the loops of Henle until the urea level of the plasma exceeds 100 mg. per 100 cc.; above 200 mg. it diminishes diuresis and edema results (Gremels, 1938).

Toxic Actions.—No effects are perceptible if the urea nitrogen of the blood is below 45 mg. per 100 cc. Loss of appetite, nausea and vomiting develop about 70 mg. (J. H. Crawford and McIntosh, 1925). Hewlett *et al.*, 1916, found that the administration of 100 Gm. of urea by mouth to man increases the blood urea to 160 to 245 mg. per 100 cc. in a few hours. This is accompanied by prostration, apathy and somnolence, symptoms resembling those that occur in pure retention uremia, when the blood urea rises to 100 to 200 mg. per 100 cc. However, nephritis may not show any uremic symptoms with 255 mg. (McLean, 1917). *Intravenous injection* of urea, 0.1 to 3.2 Gm. per Kg., in dogs causes immediate marked fall of blood pressure with cardiac slowing, followed by prolonged moderate rise of pressure, increase of heart rate and polyuria. These effects are attributed to direct stimulation of the medullary vasomotor and cardiac centers (Popesco, 1939).

Urea in the Treatment of Infected Wounds.—The strongly proteolytic action of urea, described by K. Spiro, 1900, and W. Ransdem, 1902, suggested the liberal application of urea crystals, or a saturated aqueous solution, against the foul odor of cancer (W. M. Millar, 1932), and then to other septic wounds. It deodorizes, hastens healing and does not irritate the surrounding tissue (Holder and McKay, 1937). Urea delays or hinders the clotting of blood by a solvent effect on fibrin (Foulger and Mills). It accelerates peptic and tryptic digestion *in vitro* (optimal concentration about 15 per cent), probably by an action on the protein substrate (McCawley and Gurchot, 1940).

Urea, U.S.P. (*Carbamide*), $CO(NH_2)_2$; freely soluble in water (1 Gm. in 1.5 cc.). Dose, 0.5 to 8 Gm. in solution or cachets, to a total of 15 to 60 Gm. per day for three to five days, when it should be omitted for a few days, and then repeated if necessary (H. R. Miller and Feldman, 1932). It should be taken in water, after meals, when it is not likely to cause nausea. Fantus recommends Syrup of Acacia to disguise the taste.

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CALCIUM SALTS

The insoluble calcium phosphate and carbonate serve to give hardness to the bones and teeth. Their deficiency is one of the important phenomena of rickets and osteomalacia. Pathologic calcifications of arteries and other tissues are phenomena of degeneration; their mechansim is not understood.

The soluble Ca ions are present in all tissues, and appear to be essential to the proper permeability of the plasma membrane. Excess of Ca is depressant to most nervous and muscular functions, and is antagonistic to Mg and Na. These systemic actions are produced only on excised tissue or with intravenous injection, since the absorption of Ca is slow. It has been tried, with only partial success, in various spasmodic conditions. Acute deficiency of Ca produces stimulation of these structures, most conspicuously of the central nervous system. This is seen in poisoning by oxalates, which precipitate Ca. It may also be produced by the intravenous injection of citrates or tartrates which decrease the ionization of Ca. Calcium is necessary for the coagulation of blood and for the typical clotting of milk. Calcium salts have therefore been administered in hemorrhagic conditions; but since these are not due to deficiency of Ca, the additional Ca has no effect. Calcium seems to decrease the permeability of blood and lymph vessels, and thereby to lessen exudation. It has been used against serum rashes and urticaria with variable success. Calcium chloride renders the urine acid. Calcium carbonate (chalk) is employed in diarrheas, mainly as antacid and protective. Lime water (solution of calcium hydroxide) is added to milk to increase its alkalinity. Calcium oxide, quicklime, is a slowly acting caustic, and is used as disinfectant, as is also the hydroxide or slaked lime. Calcium sulfate, plaster of

Paris, is important for its mechanical properties. The calcium salts are also used for the actions of their anions (bromide, and so forth).

The **calcium content of the body** averages about 3.8 pounds in human adults, about 99 per cent of this in the skeleton, $99\frac{1}{3}$ per cent in adult rats, and not below 98.9 per cent in immature rats raised on calcium-poor food (Bessey, King *et al.*, 1935).

The **daily requirement of calcium** for man is estimated as 0.5 to 1.5 Gm. It varies with growth and age, pregnancy and lactation; but 0.9 Gm. may be accepted as fully meeting the usual requirements of adults. The optimum probably lies above this, but is difficult to judge, as effects on growth, longevity and fertility extend over long periods, even over several generations (Sherman, Campbell and Lanford, 1938).

Adults require the daily consumption of 450 to 900 mg., averaging 750 mg., to maintain calcium equilibrium. About 300 mg. of this are not absorbed, so that the actual "stream" is about 450 mg. per day (J. Outhouse *et al.*, 1941). Childhood requires retention of Ca and of P for bone growth. The required *retention* has been estimated as 0.3 Gm. per day of Ca at one year, rising gradually to 0.5 Gm. at adolescence (Leitsch, 1937); the required *income* of children as 1.2 Gm. per day, of adults as 0.5 Gm. Older men require 0.5 Gm. of Ca and 1.2 Gm. of P per day for equilibrium (E. C. Owen, 1939). The urinary excretion of Ca of adults is remarkably constant, about 0.5 Gm., although the income varies widely (Buttner, 1939).

The **daily income of calcium,** with ordinary American diets, ranges from 0.08 to 1.7 Gm., averaging 0.85. The average is barely adequate for ordinary requirements, and would be inadequate in pregnancy and lactation. It is easily increased by drinking milk, or by diluting the table salt with an equal amount of chalk (McCollum, 1919). The entire daily requirement of 0.9 Gm. is supplied by 1 quart of milk, but would need pounds of meat or cereals. It is not generally realized that milk usually contains more calcium than does lime water (Sherman *et al.*, 1918).

A quart of milk furnishes 1.2 Gm. of calcium and 0.9 Gm. of phosphorus. The phosphate content in cow's milk is considerably higher than in human milk, both absolutely and in relation to calcium (G. Stearns, 1939). The calcium of milk seems to be more favorably retained than calcium lactate (Givens and Mendel, 1917). The utilization of the calcium of milk products averages about 29 per cent (F. R. Steggerda and Mitchell, 1941). Meat ranks next to milk in the diet as a Ca source (Krane, 1927). H. N. Green and Mellanby, 1928, reported that *wheat and other cereals* have a decalcifying effect on animals fed with a diet deficient in vitamin D; but their results may be explained by the Ca and P content of their diet. The calcium of refined flour is utilized better by man than that of whole wheat flour; the phytic acid of the bran appears to interfere with the absorption (R. A. McCance and Widdowson, 1942). Inorganic calcium salts supply the calcium needs as well as do natural foods (Osborne and Mendel, 1918).

The *appetite for calcium* (when rats are given access to calcium lactate solutions) is a sensitive index of substances that affect the calcium concentration of the blood: It increases greatly when the level is lowered by parathyroidectomy, and is decreased by dihydrotachysterol, within twenty-four hours (C. P. Richter and Birmingham, 1941).

The availability of the ingested calcium and phosphate is decreased by substances which tend to precipitate either, and is favored by those that keep them in solution. The proportion of total ingested calcium which is absorbed varies with individuals and in species (review, M. A. Logan, 1940).

For *foods*, it is said to vary directly with the Ca:P ratio, and is better for meats than for vegetables (Orr *et al.*, 1928). The calcium of carrots and spinach is poorly utilized (by growing rats), and the calcium oxalate of vegetables is completely unutilizable (McClugage and Mendel, 1918; Fairbanks and Mitchell, 1938). Feeding with cabbage tends to raise the blood calcium, and bran and oats lower it (Orr *et al.*, 1928).

The *solubility and absorbability of the chemical compounds of calcium in the gastro-intestinal tract* vary with the reaction: those that contain ionized calcium, including the bicarbonate and acid phosphate, are soluble when the reaction is acid, and are precipitated as basic salts when the reaction turns toward alkaline. They therefore tend to dissolve in the acid stomach and then remain in solution, or are precipitated at various levels of the small intestines, and are absorbed or not, accordingly. Organic calcium compounds are less subject to alkali precipitation.

Practically, the form and solubility of calcium employed make little difference in their availability, except at critical levels of vitamin D income, when calcium lactate gave better results than the difficultly soluble calcium silicate (Deobald, Elvehjem *et al.*, 1936). Rats on slightly low Ca and P income generally utilized *dicalcium phosphate* somewhat better than the tricalcic, but the difference is so small that it could only be detected under marginal conditions (Rottenstein and Maynard, 1934). In *achylia gastrica*, the absorption curve of calcium lactate or gluconate runs practically normal, and is but slightly increased by administering hydrochloric acid (J. P. Quigley, Einsel and Mull, 1936).

The excretion of calcium varies with the diet (Kochmann, 1919). Nelson and Williams, 1916, found the average daily excretion by urine and feces in man to total 0.31 to 0.73 Gm. of Ca (all ages, unrestricted diet); 0.11 to 0.36 Gm. per day is excreted by the urine, mainly as phosphate; the remainder leaves by the feces, also as phosphate, representing chiefly unabsorbed calcium. It is believed (E. Voit, 1880) that a part of the fecal Ca is absorbed by the small intestines and reexcreted by the large; but no substantial amount is excreted by the human colon (C. S. Welch *et al.*, 1936).

The amount of calcium circulated daily from the blood into the intestinal lumen and then reabsorbed into the blood may be as large as the amount absorbed from the food. The effect of acid on the excretion of calcium is appreciable but minor (it is more important in rabbits). *Ketosis* increases the urinary calcium excretion (review, M. A. Logan, 1940).

With *hypodermic injection* of calcium salts, a large part is excreted promptly by the urine, a small proportion being temporarily retained. The intestines do not always participate in the excretion. The output of Mg is also increased (Mendel and Benedict, 1909). *Intravenously injected* calcium disappears promptly from the blood, and is rapidly, but not quantitatively, excreted, chiefly by the intestines.

Calcium retention and depletion depend not only on the income, but chiefly on absorption from the intestinal tract as influenced by various conditions, including the calcium store, acid-base balance, lactation, magnesium income and various hormones, especially the parathyroid and thyroid.

Growth requires calcium retention. In preschool children, this is usually at the rate of 6 to 10 mg. per day, regardless of the ingested amount within wide limits (A. L. Daniels, Hutton *et al.*, 1935). Mendel and Osborne, 1917, found that rats require considerable calcium and phosphate for growth. The *administration of Ca* (chloride or lactate, several grams per day) increases the Ca stock of the tissues and blood, even in well fed adults (Voorhoeve, 1911 and 1913); but for a given income of Ca, the rate of Ca retention is determined by the degree to which the skeleton is already saturated with Ca; low saturation tends to favor retention (Fairbanks and Mitchell, 1936). *Acidosis* depletes the calcium of the bones and causes increased excretion (Underhill, 1916). This holds also for acid-ash food (bran and oats), while basic-ash food (cabbage) tends to retention and increase of the plasma Ca level (Orr *et al.*, 1928). Oral administration of hydrochloric acid increases the urinary excretion of Ca and Mg (Stehle, 1917). Alkalis do not decrease the urinary Ca output in human diabetes (Givens and Mendel, 1917).

The *relations of magnesium and calcium excretion* appear complex. In human urine, either Ca or Mg may predominate, this being fairly constant for the individual, and largely independent of the food (Nelson and Burns, 1916). The administration of soluble Mg salts increases the urinary excretion of Ca, but not if phosphates are present in the alimentary canal (Hart and Steenbock, 1912). Becka, 1929, reported that $MgCl_2$ caused primary retention of Ca, followed by increased urinary excretion; that $MgSO_4$ caused loss of Ca by the feces; and $Mg(OH)_2$ caused retention. *Lactation* depletes the Ca stock, in cows, even when Ca is added to the food (Forbes *et al.*, 1917). *Hyperthyroidism* increases Ca excretion, by feces and urine, more than any other condition, so that the output may be four or five times the normal; it is lowered in thyroid deficiency. The serum calcium level is normal in both conditions (Aub, 1937), but Graves' disease causes a marked negative calcium balance, with decalcification of the bones, especially the spine. The *parathyroid relation* will be discussed in a separate section.

Calcium Content of Blood.—The corpuscles contain little calcium, so that there is a marked difference between the calcium content of the whole blood and that of the serum. The calcium concentration of human erythrocytes is 0.1 to 1.4, average 0.2 milliequivalents per liter (Hald and Eisenman, 1937); that of the serum or plasma, on the other hand, is remarkably uniform, 4.5 to 5.7, average 5.2 milliequivalents per liter (E. Kirk *et al.*, 1935), between 9 and 11 mg. of Ca per 100 cc. even in most pathological conditions (Halverson *et al.*, 1917). It is not easily altered, except temporarily, because the plasma is saturated with calcium, for normal conditions, and is kept so by the precipitation of any excess as phosphate; and by the replenishment of any deficiency through solution of the calcium of trabecular bone, which acts as reservoir. The solubility of calcium in the plasma is determined by the ratio of carbonate and phosphate, and by the *p*H, increase of carbonate and acidity being solvent, excess phosphate and alkalinity being precipitant. Brief alterations of these conditions may be produced by the injection of calcium salts, more lasting alterations by viosterol and parathyroid hormone, and by their deficiency.

Calcium gluconate, administered by mouth in the clinical dosage of 2 Gm. in 20 cc. of water, raises the Ca level of the serum to a peak level of 15 mg. per 100 cc. in about four hours, returning to normal in about the twelfth hour. With intramuscular injection, the same dose reaches a peak of 19 mg. in an hour, and the normal in the eighth hour (Lieberman, 1931).

The Condition of Calcium in the Blood Plasma.—Of the normal 9 to 11 mg. per 100 cc., about half to two-thirds (5 to 6 mg.) is *diffusible; i. e.*, it is in diffusion equilibrium with solutions of ionizable calcium salts of this concentration (Rona and Takahashi, 1911). The ultrafiltrate of serum also contains about half of the calcium. Determination of the calcium ion content of serum and other fluids by the effect on the isolated frog heart also corresponds to about 5 mg. per 100 cc., so that this part of the calcium may be considered as ionized (McLean and Hastings, 1935). The remaining third to half, which is *not diffusible* or ultrafiltrable, exists almost entirely as protein salts and is ordinarliy proportional to the protein concentration (Salveson and Linder, 1923).

An insignificant part of the calcium exists as diffusible nonionized compounds, similar to the calcium-sodium citrate. None of the indiffusible calcium appears to be in lipid combination, for none is extracted by ether; nor in combination with phosphate, for all the serum phosphate is filtrable (Grollman, 1927). The distinction between diffusible and nondiffusible calcium is not sharp, for the protein salts furnish ionized calcium, and vice versa, if the equilibrium is disturbed by lowering or increasing the total calcium content.

The entire calcium of serum diffuses into isotonic sodium chloride solution, and 90 per cent is precipitated by m/320 oxalate. About 5 per cent of the calcium of the plasma is in nonionized but diffusible form (Logan, 1940). Moderate increase of serum calcium by intravenous injection of small amounts of calcium salts, or by parathyroid administration, is almost exclusively in the diffusible fraction; but larger increases extend also to the nondiffusible (Greenberg and Tufts, 1934). The normal ratio is restored in one or two days (Moritz, 1926). In the protein-poor *cerebrospinal fluid*, the calcium (5 mg. per 100 cc.) is practically entirely diffusible (Salveson and Linder) and corresponds to the ionized calcium of the serum (McLean and Hastings). The calcium of *milk*, which is about ten times as high as in blood plasma, exists about a fourth as undissociated calcium caseinate, and three-fourths as colloidal calcium phosphate (N. C. Wright, 1928).

Organic Calcium Complexes.—Ca, Ba and Sr form reversible nonionized molecules with many organic acids, such as citric, tartaric, succinic, lactic, acetic, phthalic, benzoic and salicylic. These do not produce the calcium ion effects, for instance on frog heart (N. R. Jacobs, 1946).

Effects of Phosphate on Calcium Solubility.—The ionized calcium of the plasma is balanced by Cl′, HCO'_3 and HPO''_4 anions. The solubility of the bicarbonate, which is probably the chief form (Halverson *et al.*, 1917), is limited, and the phosphate is even less soluble. The solubility, that of the phosphate especially, decreases by the formation of basic carbonate and phosphate, if the H ion concentration is lowered. The plasma is ordinarily fairly saturated with calcium for the existing conditions. In Ringer's solutions buffered with bicarbonate and phosphate in imitation of the plasma, calcium phosphate is precipitated by aeration, which removes CO_2 and tends to render the solution more alkaline; or by increasing the proportion of phosphate ions (Sollmann, von Oettingen and Ishikawa, 1928). Corresponding conditions tend to lower the calcium concentration of the plasma and vice versa. The calcium changes of parathyroid hormone, *f. i.*, seem to be secondary to changes in the plasma phosphate level.

Detailed studies of the reactions of alkali carbonates with calcium phosphates have been made by H. J. Wichmann, 1943. PO_4 increases the solubility of $CaCO_3$; HCO_3 increases the solubility of calcium phosphates (I. Greenwald, 1945).

Addition of sodium phosphate to serum *in vitro* lowers the calcium in solution by the formation of a colloidal complex of Ca and PO_4. This occurs also on intravenous injection and even on oral administration of soluble phosphates (F. C. McLean and Hinricks, 1938). The colloidal calcium phosphate is quickly removed from the circulation by phagocytosis in the liver and spleen (Gersh, 1938). Even tertiary calcium phosphate, $Ca_3(PO_4)_2$, which is practically insoluble in water, precipitates calcium carbonate from serum (Sendroy and Hastings, 1927). On the other hand, unsaturation of calcium, *f. i.*, by acidosis or by decrease of phosphate, would be made good by solution of the calcium stores of the bone trabeculae. *Calcification*, on the other hand, is probably due to local increase of phosphate ions, liberated from lecithin by phosphatase at the site of calcification (Robison). Sodium hexametaphosphate disionizes calcium without precipitation. The addition of *citrates* disionizes calcium, as shown by conductivity measurements, as well as by the masking of the ordinary calcium reactions. Acetates and lactates do not have this effect (Shear, Kramer and Resnikoff, 1929). *Naphuride* (Germanin) also disionizes calcium by forming a complex, and so prevents blood coagulation (Mulli *et al.*, 1933).

Disturbances of the plasma calcium level are characteristic for several pathologic conditions. In *rickets* there is a slight but distinct decrease (Howland and Marriott, 1917). In *tetany*, the plasma calcium falls to 3 to 5 mg. per 100 cc. This is counteracted by measures that increase the acid-alkali balance of the body, *i. e.*, by the administration of acids, ammonium chloride or calcium chloride. The calcium level of the blood may be materially raised by the injection of the parathyroid hormone; the level falls if the parathyroids are excised. *Hyperglycemia*, diabetic or by dextrose injection, tends to raise the plasma Ca by decreasing the inorganic phosphate of the plasma (by synthesis of phosphate ester).

Calcium chloride injections prevent the glycosuria and fever of NaCl injections, but large doses of $CaCl_2$ may themselves produce glycosuria (Underhill and Kleiner, 1908). In *phlorhizin glycosuria,* Jacoby and Rosenbloom, 1915, found that large doses of calcium diminish the excretion of sugar, nitrogen and acetone. The blood sugar is also lowered, so that presumably the production of sugar is diminished. *Calcium therapy in phthisis* was recommended by Fourcroy, 1783. It has been tried repeatedly, on the assumption that phthisis is accompanied by excessive excretion of calcium. This has been affirmed by some competent observers, but does not appear to be an invariable phenomenon (Kahn, 1914). Mohler and Bergeim, 1917, found no characteristic changes. The clinical reports are too discordant to justify faith in this treatment. The intravenous injection of 5 cc. of 5 per cent calcium chloride against *intestinal tuberculosis* was introduced by Saxtorph, 1918. According to Fishberg, 1919, it relieves the diarrhea and pain in minor grades. It is ineffective in the severer grades, and is at best only palliative. The plasma phosphate is reported normal in *asthmatic conditions* (Criep and McElroy, 1928, 167 patients) and after *splenectomy* or injection of spleen extract (Underhill and Gross, 1929; contradicting Hall and Abderhalden). Moraczewski, 1900, claimed considerable loss of Ca in *pernicious anemia.*

Functional Variations in the Plasma-Calcium Level.—*Age,* between twenty and ninety years, does not show any correlations (Kirk, Lewis and Thompson, 1935). *Pregnant women* show a slight decline of the plasma Ca level from 10.4 to 9.9 mg. at eight weeks before term, with recovery to 10.0 mg. by term. This is maintained even with nursing, to dismissal at six weeks post partum. The plasma phosphate shows nearly parallel changes during gestation, with a marked rise after delivery. The phosphatase is generally within the normal range to the seventh month, then increases progressively to 80 per cent above the normal in the last month. The *fetal blood* has distinctly higher levels of Ca and P than the maternal blood drawn at the same time. The serum Ca at birth is usually 11 to 13 mg. per cent (G. Stearns, 1939) and drops distinctly during the first four days after delivery, then rises slightly above the average of later infancy (Mull and Bill, 1934; Mull, 1936; Bodansky, 1939; Denzer *et al.,* 1939). In *cows,* Meigs, Blatherwick and Cary, 1919, found the plasma calcium between 8.6 and 11 mg. per 100 Gm., practically unaffected by pregnancy, lactation or considerable changes of diet (in very young calves, however, it is higher, up to 13.7 mg. per cent). Emmerich and Loew, 1915, observed that administration of calcium to female mice, guinea pigs and rabbits was followed by increased *fertility,* a greater number of pregnancies and higher averages of the feti. The *depletion* of the mother's body during pregnancy amounts to 6 per cent of the total calcium, in rats (Mull, 1936). Lactation causes 2 to 28 per cent decrease of the body calcium, practically all derived from the skeleton (H. C. Sherman and McLeod, 1925). The Ca and PO_4 of the fetus do not come from the *teeth,* and these show no more change than in parallel observations of nonpregnant women (Mull, Bill and Kinney, 1934).

Egg shell formation in birds requires large amounts of calcium carbonate, about a kilogram per hen in the laying season. About 5 Gm. of $CaCO_3$ are deposited in the shell by the cells in direct contact with the egg. The deposition begins as soon as the egg reaches the uterus, and continues during most of the twenty to twenty-four hours' sojourn of the hen egg, the shell being quite rigid about thirteen hours before laying. Phosphatase does not appear involved in the deposition, as the alkaline phosphatase content of these shell glands is low (M. S. Gutowska *et al.,* 1943). Carbonic anhydrase appears essential, for egg shell formation is arrested by sulfanilamide, which inhibits carbonic anhydrase (Keilin and Mann, 1944), and not by sulfapyridine, which lacks this effect (Benesh, Barron and Mawson, 1944); but R. Bernard and Genest, 1945, consider the evidence inconclusive. The blood serum calcium level of laying hens is two or three times higher than that of nonlaying hens or of males (review, R. M. Conrad and Scott, 1938). A similar rise occurs in ovulating pigeons, beginning some days before egg shell secretion starts. The calcium is supplied both from the food and from the skeleton. The addition of calcium salts to the ordinary feed of pigeons does not materially influence the amount of calcium in the egg shells, but egg laying ceases if the food calcium is deficient (review, W. U. Gardner and Pfeiffer, 1943). Abrupt withdrawal of calcium from the diet of laying hens lowered their bone ash by 10 per cent, and the shells had only 25 per cent of the normal ash content (Deobald *et al.,* 1936). Injection of *estrogenic hormones* into birds raises their serum calcium level and accelerates formation of endosteal bone, probably by stimulation of the osteoblasts and not by calcium increase (review, W. U. Gardner and Pfeiffer, 1943).

Distribution of Ca in Cells.—Calcium is present in practically all cells and tissues. Only a few of the lower fungi are able to live without it. The calcium (also magnesium) is concentrated in the nucleus, the cell membrane, the anisotropic discs of striated muscles, the zymogen granules of the pancreas, and definite locations of some epithelial cells. It appears to be nondiffusible, presumably bound to proteins (G. H. Scott, 1943). Animal cells are covered with a protein-like coating which is stiffened by calcium. The essential plasma membrane is within this coating and does not require calcium for its maintenance (R. Chambers, 1942). *Red blood cells* contain calcium in all mammals studied, as well as in man. The content of human corpuscles is about 1.6 mg. per 100 Gm., about a third to a half of their Na content (Streef, 1938). The calcium content of *skeletal muscle,* in animals on normal Ca intake, does not increase when the Ca or vitamin D income is increased. Tetany (in kittens) is not preceded by significant change in the muscle calcium; nor are guanidine convulsions in rabbits. Parathyroid excision gave variable results (Burns, 1933). In mammalian *smooth muscle,* the calcium and magnesium are almost entirely within the muscle cells, little in the tissue spaces (G. H. Scott, 1940; electron microscope). *In the skin,* calcium is more abundant in the epidermis than in the cutis, as is also potassium (Kooyeman, 1935).

Calcium in Bone.—Normal mature bone contains somewhat less than half its weight of water, and fat up to 25 per cent. Of dog fat-free bone, 30 to 40 per cent is organic, the remainder inorganic, consisting practically entirely of $Ca_3(PO_4)_2$ and $CaCO_3$, generally in the ratio of $\frac{1}{2}$–3:1, generally 3:1. This corresponds to the *apatite* group of minerals (Hoppe-Seyler), either $3Ca_3(PO_4)_2 . CaCO_3$; or $3Ca_3(PO_4)_2 . Ca(OH)_2$, with some $CaCO_3$. The evidence is not decisive, but probably both are present- and other ions may take the place of the $(OH)_2$, for instance fluoride, giving "*multiple apatites,*" $nCa_3(PO_4)_2$ CaX'', where X″ may be O, Cl_2, SO_4, CO_3, F_2, and so forth, or mixtures of these (Taylor and Sheard, 1933).

Calcium Phosphates.—Primary calcium phosphate $Ca(H_2PO_4)_2$, is very soluble, but does not exist at the *p*H range of animal fluids. Secondary calcium phosphate, $CaHPO_4$, and the tertiary phosphate, $Ca_3(PO_4)_2$, are difficultly soluble, but hydrolyze readily to form hydroxy apatite $3Ca_3(PO_4)_2 \cdot Ca(OH)_2$ (Bassett), which is a stable solid phase over a wide range of *p*H of biologic significance (Huggins, 1937, review). Blood plasma is practically saturated with calcium bicarbonate and dicalcium phosphate (H. G. Wells, 1906). Serum dissolves 475 per cent more $CaCO_3$ than does water, and 90 per cent more $Ca_3(PO_4)_2$. This relatively high solvent power is due partly to the CO_2 tension, partly to the proteins, which act as protective colloids. Both may be readily altered, for instance by local changes of reaction, or by local autolysis of the proteins. The latter decreases the solubility of the phosphate more than that of the carbonate, so that the phosphate would be precipitated more readily. This agrees with the fact that bone contains about nine times as much of the phosphate as of the carbonate of calcium (Pauli and Samec, 1909). The precipitation of calcium in the presence of colloids was investigated by Sabbatani and Salvioli, 1912.

Bone Calcium.—The *ratio Ca:P::1:0.6* is nearly uniform in all bone, normal or pathological, including the bone of rickets and of phosphate deficiency. The *carbonate fraction* varies much more than the calcium phosphate. It increases with age (in rats and in cattle; Kramer and Shear, 1928; Neal, Palmer *et al.*, 1931). It is decreased in acidosis and increased in alkalosis (Huggins, review, 1937). *X-ray diffraction studies* of normal bone show the micellae arranged longitudinally in the shaft, but it is not certain whether this is due to crystalloids or to the collagen or ossein (J. H. Clark, 1931; Bogert and Hastings, 1931). This orientation is largely destroyed in rickets, probably by the breaking down of the collagen. On healing, inorganic micellae do not regain the regular orientation, and the bone remains weakened (G. L. Clark and Mrgudick, 1934). *Proper deposition of calcium in the formation of bone is* influenced by several factors: (1) endocrine glands, especially the parathyroid, thyroid, pituitary and sex glands; (2) vitamins, especially D and C; (3) the supply of Ca and PO_4; (4) acid-base balance (review, M. A. Logan, 1940). *Renovation of bone* goes on continuously, especially in the trabeculae. By feeding *radioactive P isotope,* Chievitz and Hevesy, 1935, determined that in adults some 30 per cent of the P atoms of the skeleton were removed and replaced in twenty days. The exchange is more lively when extra calcium is mobilized in pregnancy, lactation, acidosis, or by the parathyroid hormone (G. C. Hevesy *et al.*, 1940). On *intravenous injection of radioactive calcium or strontium lactate,* a third to a half is found in the skeleton after twenty-four hours. Their concentration in newformed bone may be a hundred times more than in soft tissues. It is highest in the roots of teeth and in trabecular bone, lowest in liver and fat (C. Pecher *et al.*, 1942). It has been suggested to use such radioactive injections in treating cancerous bone.

Radioactive carbonate, injected into rats as sodium or barium carbonate containing C^{14}, appears primarily in preexisting bone, rather than in the currently deposited bone, showing that the old bone entertains an active exchange. It does not decrease appreciably in the bone within four months, indicating that it may result in radiation bone lesions (W. Bloom *et al.*, 1947).

Feedings *dyes,* as alizarin and related anthraquinones (madder dye), stains new bone by forming calcium lakes, while old bone is but little stained. Lithium carmine and trypan blue stain the organic material of new bone, so that the color persists after decalcification of the specimens (review, C. Huggins, 1937).

Calcium-deficient diets stunt bone growth in young animals, and lead to a form of rickets. The bones contain about the normal percentage of lime; but little bone is laid down, and this is thin, pliable, deformed and fragile (E. Voit, 1889). It contains more water, Na and K, while the Mg is not materially increased. The percentages vary, however, in different parts of the skeleton. The animals are undersized, with poor appetite and defective nutrition (Weiser, 1914). *Low phosphate intake* decreases the ash content of bone; but the Ca:P ratio of bone is not materially altered by either Ca or P deficiency. In rabbits, the Ca content of the bones is increased by green food, diminished by exclusive *oat diet* (Luithlen, 1912). The "*decalcifying effect*" *of cereals* was also emphasized by E. Mellanby, 1926. It is probably due to faulty Ca:P ratio, for cereals are low in available phosphate, since 30 to 70 per cent of the P of grains exists as *phytin,* which is poorly utilized by man and by rats (Report of Committee on Foods, J.A.M.A., 1937, *109:* 30). *Sodium oxalate,* administered for a week, diminishes the Ca content of the soft tissues before it affects the bones (Sarvonat and Roubier, 1911). If this diet is rich in magnesium, the bones may accumulate double the normal Mg content, without improving the skeletal development. *Lactation* causes marked loss of bone calcium (Sherman and McLeod, 1925).

Storage of Other Metals in Bone.—Trabecular bone is the chief storage magazine of elements whose chemical properties resemble those of calcium. This has been demonstrated for lead, radium, thorium, polonium, and holds doubtless for strontium and barium. Bone and tooth are also the chief depositories for fluoride. Lead and the other bases are mobilized by the same agencies that mobilize the bone calcium, such as acidosis (ingestion of H_3PO_4 or NH_4Cl); and by the administration of parathyroid hormone (Hunter and Aub, 1927).

The calcium of teeth is also of the *apatite* model (Brekhus and Armstrong, 1934). That of the enamel is mostly of the calcium hydroxide form, with the Ca:P ratio of about 2:15; that of the dentine with 2.09 ratio, probably containing some $CaHPO_4$, more carbonate, and twice as much Mg as the enamel. Only traces of K, F or Si are found in either (Bowes and Murray, 1935; Armstrong, 1935). *Mature erupted teeth* are not affected in calcium content or in structure by changes of the calcium or phosphate income, of the general calcium metabolism, or by viosterol (Schour, 1938). The *phosphate metabolism* of developed teeth is small, requiring about eight months to exchange 1 per cent for radioactive isotope, and $\frac{1}{8}$ to $\frac{1}{10}$ per cent with the enamel (G. C. Hevesy and Armstrong, 1940). Unlike bone, neither dentine nor enamel functions as storehouses of calcium, and they are not subject to calcium withdrawal, for instance in pregnancy (Kinney, Mull and Bill, 1932), or on parathyroid administration. Tooth decay and caries are in no way connected with calcium metabolism; nor with the chemical solvent action of saliva (Brekhus and Armstrong, 1934). *Immature,* *growing and calcifying teeth* may easily be affected by changes in the calcium metabolism, by diet, vitamins and endocrines; and the changes initiated at this time may influence the resistance of the adult tooth. Most of the evidence is derived from the incisors of rats, which continue to grow throughout life; it is therefore questionable whether they can be transferred directly to the human. Schour, 1938, believed that they correlate well; the Committee on Dental Therapeutics (J. Am. Dent. Ass., 1936, *23:* 139) believes that there is no decisive evidence that the addition of Ca or PO_4 to a normal diet has any definite effect on the incidence of dental decay for adult, child or fetus. Since the calcification of human teeth is entirely postnatal, it would not be affected by the Ca or P income of the mother during gestation (A. F. Hess and Roman, 1932); but I. G. Macey *et al.*, 1930, reported that large doses of Vitamin D during pregnancy tend to promote tooth development and to prevent later caries. The density of enamel and dentine increases with age (review, J. A. Marshall, 1939).

Phosphatase.—The actual deposition of calcium in bones is apparently due to the local activity of phosphatase, which splits off inorganic phosphate from hexose phosphate and other phosphoric esters, such as glycerophosphate (Martland and Robison, 1924), thereby raising the PO_4 to the level where calcium phosphate is precipitated. This occurs *in vitro* when the Ca × P in the serum or Ringer's solution exceeds 30 mg. per 100 cc., practically regardless of the ratio of the two elements to each other. At this level calcium is deposited *in vitro* in ossifying rachitic cartilage (Shipley, Kramer and Howland, 1928). Slices of rachitic bone do not deposit calcium when laid in Tyrode solution with the Ca and PO_4 concentration of plasma, but addition of phosphate esters leads to marked calcification, resembling the normal healing of rickets. Addition of NaCl, KCl and especially of Mg (1 to 2 mg. per 100 cc.) necessitates higher concentrations of PO_4 and Ca in the Ringer solution (Shelling, Kramer and Orent, 1928). Addition of bicarbonate favors Ca deposition, indicating that the deposit is a Ca phosphate-bicarbonate salt. Protein and glucose raise the concentration of Ca necessary, probably by the disionization of Ca.

Phosphatase is widely *distributed* through the tissues in cartilage, kidneys, intestines and blood plasma, but its concentration is especially high in the ossifying centers of actively calcifying bone; for instance, epiphyseal junction contained forty-six times as much as costal cartilage (Robison). It rises rapidly at the site of fracture in broken bone, to eighty times the normal, and remains high till the repair is completed (W. E. Wilkins and Regen, 1935). Viosterol administration tends to lower the phosphatase content of the plasma, coincident with the rise in plasma calcium (Crimm and Strayer, 1936, 1937). The *phosphatase level of the blood serum* is increased in diseases of the bone, especially if osteoblastic activity is increased as in rickets, where it may rise to twenty times the normal. This increase is one of the earliest and most delicate signs of rickets, going fairly parallel with the progress of the disease and regressing with its cure. Increase of phosphatase also occurs in osteitis deformans and in jaundice (H. D. Kay, 1930; A. Bodansky, 1933).

There are *several phosphatases* grouped according to the reaction of their optimal activity, as alkaline about *p*H 9, and acid about *p*H 5. *Alkaline phosphatase* is by far the more widely distributed. It is the form concerned in the formation of osseous tissue and is probably involved in the absorption of dextrose from the intestines and its reabsorption from the renal tubules. Its activity is enhanced twenty- to forty-fold by Mg ions; that of acid phosphatase is not (Bamann and Riedel, 1934). *Acid phosphatase* occurs chiefly in the liver and kidneys, and is involved in glycolysis by acting on hexose phosphates. It is abundant in human prostatic secretion, being formed by normal and cancerous prostatic epithelium, and serves as an index of prostatic activity and therefore of androgen. It is increased in the blood serum of patients with bone metastases of prostatic carcinoma. Castration or administration of estrogens is used to inhibit this condition (Huggins, 1943).

Degenerative calcification is a common pathologic process, especially in connective tissue. The calcified areas are generally dead (except those that have the structure of bone). The lime deposits in the dead tissue have usually the same proportion of lime salts as bone, about 87 per cent of phosphate, and 10 to 15 per cent of carbonate. The mechanism of calcification is not understood. Wells (1906) found that certain substances, including dead cartilage, when introduced into the tissue of rabbits, accumulated rather large quantities of calcium, indicating a direct physical or chemical affinity. MacCordick, 1913, found the rigidity of *calcified arteries* different during life from after death, and therefore suggested that the Ca is in solution during life, and deposits in the plaques after death.

Rickets.—Disorders of the Ca and PO_4 equilibrium of the blood are responsible for rickets and osteomalacia. Clinical rickets is caused by deficiency of vitamin D (ultraviolet irradiation, or its product, viosterol), leading to defective bone calcification and various systemic disturbances, which may include spasmophilia if the plasma-calcium level is low. The percentage of mineral substances, and particularly the calcium phosphate in the abnormal proliferation bony tissue, is materially reduced, sometimes to half of the normal, but the Ca:P ratio remains practically unchanged. The immediate cause of rickets is a low Ca × P product in the plasma. Ordinary human rickets is "low P rickets," due to disturbance of the phosphate metabolism, and not of the calcium. The calcium income may be abundant (Stoelzner, 1899) and the Ca:P ratio of the diet may be normal; the absorption and excretion of calcium are practically normal (Ruedel, 1893); the calcium level of the blood is but little decreased (Howland and Marriott, 1917). The condition is prevented and cured by the antirachitic vitamin, by sunlight and by ultraviolet light. The administration of calcium salts has little effect (M. Klotz, 1915).

Ca × P Product of the Plasma and Body Fluids.—**Disorders of calcium and phosphate metabolism fall into**

three groups (Albright, Bauer *et al.*, 1931): (1) *Low Ca × P* results in failure to deposit calcium phosphate in the osteoid matrix, and produces rickets or osteomalacia. The C × P of human plasma is normally about 50 mg. per 100 cc., made up of about 10 mg. of Ca and 5 mg. of P. Active rickets develops if the product falls below 30; healing sets in when it rises to 40 and becomes complete above 50 (Howland and Kramer, 1922). In incomplete treatment, the P rises before the Ca is accommodated, resulting in lowering of the Ca (by precipitation?), giving "low Ca rickets" and spasmophilia (Gerstenberger). (2) *Ca × P product above normal* occurs in viosterol poisoning. Calcium phosphate is deposited in tissues other than bone. (3) *Normal Ca × P product* with abnormal Ca:P occurs in parathyroid deficiency or excess.

Calcium and Phosphate Excretion.—In clinical rickets, the fecal excretion of calcium is increased, the urinary decreased. The fecal phosphate excretion is markedly increased (Shohl, 1938).

Rat rickets resembles human rickets closely as to the histologic picture, the low P:Ca ratio and the curability by vitamin D or ultraviolet light. They differ in that rickets develops in rats only if there is a great disproportion in the Ca:P income, in addition to the vitamin D deficiency (McCollum *et al.*, 1921). There are some further differences of minor significance (Shohl, review). *Salts of other earths and metals* (Be, Mg, Sr, Fe, Pb, Tl), which hinder adequate utilization of Ca or P (Rehm and Winters, 1940, ferric chloride), cause rickets in rats (McCollum *et al.*, 1921) and in puppies. J. H. Jones, 1935, reported that beryllium rickets of puppies is not prevented by vitamin D. Manganese also produces rickets in rats on low P:high Ca diet, which is cured by vitamin D only if the diet is made optimal in Ca and P (Blumberg, Shelling and Jackson, 1938). *Puppies*, like children and unlike rats, develop rickets on vitamin D deficiency without great distortion of diet; if the vitamin D deficient diet of dogs contains a normal P:Ca ratio, osteoporosis results; if it is alkaline, it gives paradentosis; if it is low in Ca, it gives paradentosis and osteitis fibrosa (A. F. Morgan, 1934). In *osteomalacia*, the bone contains but 20 to 40 per cent, instead of the normal 56 to 60 per cent of inorganic salts, their place being taken by new-formed osteoid tissue. The condition is due to excessive destruction of bone tissue and may occur with high Ca and PO_4 income. Limbeck, 1894, found the excretion of Ca, especially by the intestines, to exceed the income. Neumann, 1896, also found the excretion high, especially in the early stages, when the Ca of the bones is still high. The later stages may show retention. Vitamin D changes the balance of Ca and P to positive, but large doses are necessary (Blumgart *et al.*). *Infantile scurvy* shows a decided decrease of blood calcium, although not so much as in rickets. This is associated with slight acidosis. There is no tendency to tetany (A. F. Hess, 1919).

Systemic Actions.—Calcium ions are important for the irritability of the nervous and muscular systems, somatic and autonomic. Their effects are complex, depending largely on the Ca:K ratio, and are modified by the Na and H ion concentration. In general, predominance of Ca resembles parasympathetic, and of K, sympathetic stimulation, but not always. Ca quiets activity so as to render it more regular and vigorous, with longer survival of excised organs. Excess of Ca ion depresses, deficiency exaggerates, excitability; both modify the responses to stimulation by drugs or other means, but the details vary for different tissues. Intact animals also are depressed by excessive Ca concentration of the plasma, whether it is induced acutely by injecting calcium salts, or more slowly and persistently by parathyroid hormone; conversely, decrease of the Ca ion concentration of the plasma, by parathyroid deficiency, or by the injection of the anions (oxalate, and so forth) that disionize calcium, produces tetany and increased excitability of the autonomic system (vagus, depressor, and so on). Loss of total Ca by acute hemorrhage does not have this effect (Schafir, 1915), since it does not lower the calcium concentration of the plasma. Calcium ions are essential in the *coagulation of blood and of milk.* They appear to mitigate acute inflammation and edema. Calcium chloride renders the urine acid, by converting a large part of the Ca into insoluble basic phosphate in the intestines. Hypodermically, calcium chloride acts as a corrosive irritant. This is avoidable by the use of the less ionized organic salts, such as the gluconate, but even this is likely to lead to abscess formation in infants if it is injected intramuscularly (S. S. Lamm, 1945).

Calcium functions in the *extraneous coat of cells* in animals and plants. It stiffens the surface cytoplasm, and decreases the viscosity of the interior cytoplasm. In its absence the constituents disperse in the surrounding medium (M. E. Reid, 1943).

The *antagonism of Ca and Mg* has been discussed (see Index). It should be remembered that the actions of Ca are conditioned on the ratio of other ions. Thus, the intravenous injection of Ca which is depressant to normal animals, causes recovery of an animal anesthetized with Mg. Strontium does not have this effect (Meltzer, 1909).

Inactivation of Calcium.—The Ca in the body fluids, and presumably in the cells, can be rendered inactive by the introduction of precipitant anions, such as the oxalates or fluorides; or by decreasing its ionization with sodium citrate or tartrate (Sabbatani, 1902), or hexametaphosphate. In the isolated heart, the toxicity is greatest for citrate, then oxalate, then tartrate (Salant and Hecht, 1914). The inactivation produces the opposite effects from Ca, viz., excessive stimulation, convulsions, hypersensitiveness of the autonomic nerves and rhythmic contractions. These effects may be promptly removed by the addition of Ca and less efficiently by Sr and Mg (Starkenstein, 1914); but not by other cations, not even by those (Ba, and so forth) which precipitate the oxalate. The stimulation is therefore not due to the oxalate, and the like, as such, but to the inactivation of the Ca. This is confirmed by the observation that equimolecular solutions of the different inactivators have practically equivalent effects (Starkenstein). However, Salant and Hecht, 1914, found in perfusion of the isolated heart that calcium citrate or tartrate solutions act practically the same as equimolecular calcium chloride.

Toxic effects of calcium salts occur only with parenteral administration. This is used clinically in parathyroid tetany, most safely as the gluconate hypodermically.

Smaller injections, 0.06 to 0.09 Gm. of the chloride or acetate per Kg., in cats or dogs, are followed by characteristic impairment of the equilibrium and postural reflexes of the skeletal muscles. The intravenous "reactions" may be in part colloidal, owing to the formation of colloidal $Ca_3(PO_4)_2$ (Heubner, 1924). *Hypodermic injections* have similar, but much slower, actions. Animals die of central paralysis a few days after the hypodermic injection of 0.3 to 0.4 Gm. of $CaCl_2$ per kilogram. Oral administration does not produce these systemic effects.

Respiration.—Schlick, 1911, described apparent stimulation in anesthetized mammals. Haffner, 1913, found that this is indirect, because of failure of circulation from cardiac depression. The direct action is respiratory depression, which may be the cause of death. The *perfused respiatory center of frogs* is depressed by decrease of Ca, stimulated by absence or excess of Ca (Hooker, 1913). *Excised bronchial muscle* is constricted by Ca or Sr, though less than by Ba (Trendelenburg, 1912). Calcium arrests pituitary asthma (Kayser, 1914).

Circulation.—Slow intravenous injection of calcium chloride solution produces, successively, vagal bradycardia, ventricular arrhythmias, ventricular fibrillation, with only minor changes in the blood pressure, until terminal cardiac failure occurs rather suddenly (H. E. Hoff *et al.*, 1939; A. W. Winkler *et al.*, 1940). Small doses, intravenously, sometimes increase the blood pressure and heart rate slightly, by brief depression of the vagi; larger doses paralyze the vagi, but diminish the heart rate and blood pressure, by a mixed effect on the cardiac muscles and nerves (Cazzola, 1913). The small doses may considerably increase the output of the heart without changing the rate, *i. e.*, by increasing the amplitude (Rothberger and Winterberg, 1912).

Electrocardiograms are altered by the rapid injection of 10 cc. of 20 per cent calcium gluconate into the cubital vein in man. The heart rate is then markedly slowed. The T wave is almost flattened or inverted, also often the P wave. Occasionally subjects respond with premature ventricular beats, sinus arrhythmia and sinus arrest (K. Berliner, 1936). The effects of intravenous therapeutic doses are transitory. The earliest resemble vagus stimulation, but there may also be direct increase of the excitability of the ventricular muscle, foci of idiopathic ventricular contractions, and ventricular extrasystoles (N. E. Clarke, 1941). Slow intravenous injection of dilute calcium chloride into *dogs* produced successively: (1) At concentration of 15 to 65 mg. of Ca per 100 cc. of serum, slowing, often with changes of the T wave and AV conduction. (2) At 25 to 90 mg., acceleration, often ending in ventricular fibrillation. (3) At 70 to 190 mg., second slowing, with cardiac depression ending in arrest without ventricular fibrillation. Animals that survive the acute experiment may die later from unassigned causes (H. E. Hoff *et al.*, 1939). In anesthetized *rabbits*, intravenous injection of 10 per cent $CaCl_2$ at the rate of 2 to 6 cc. per minute, results in AV block, auricular fibrillation, ventricular extrasystoles and cardiac arrest. Atropine prevents the block and auricular fibrillation, but not the other irregularities. Amytal, in narcotic doses, suppresses the arrhythmias (H. E. Hoff and Nahum, 1937). *In complete heart block* injections of calcium (or barium) produce attacks of temporary arrhythmia and ventricular tachycardia, increasing to fibrillation. These attacks may be preceded by groups of powerful and rapid beats. The auricles are affected in the same sense, but not so greatly. The blood pressure rises (Van Egmond, 1913). In perfusion of the isolated fibrillating heart of dogs, increase of calcium dilates the *coronary vessels* (L. N. Katz and Lindner, 1919).

Cardiac Synergisms.—The calcium concentration of the blood modifies the circulatory reactions considerably to atropine, pilocarpine, and so on (Salant, 1924). The most important is a marked synergism with digitalis, which renders it dangerous to inject calcium solutions into digitalized patients.

Digatalis and Calcium Synergism.—O. Loewi, 1917, called attention to this danger. W. D. M. Lloyd, 1928, reported complete cardiac arrest from intravenous injection of 4 cc. of 10 per cent calcium chloride, resuscitated with epinephrine and cardiac massage. Two clinical deaths were reported by Bower and Mengle, 1936, who confirmed that the fatal intravenous dose of calcium gluconate for dogs is lowered 30 to 40 per cent by digitalization. La Barre and van Heerswynghels, 1939, found it lowered by a third in cats. Conversely, disionization of calcium by sodium hexametaphosphate restores chick hearts arrested by digitalis (Paff, 1940). In *perfused frog hearts*, absence of calcium from the perfusing fluid does not appear to interfere with the typical action of epinephrine, agaricin, saponin, strophanthin or veratrine.

Calcium on Heart Muscle.—On excised frog heart, Ca antagonizes both the toxic action of Na and the inhibitory action of K. *Deficiency of Ca* in Ringer's solution below 0.43 millimolar depresses the contractions, and absence of Ca promptly arrests them, through the predominance of the K ions. The effects are so rapid as to suggest that they must be exerted on the plasma membrane. *Other earthy metals*, Ba, Sr, Ca and radium emanations act similarly. Low concentrations increase the diastole, to diastolic standstill. Higher concentrations increase the systole to systolic standstill (Kionka, 1914). *Increase of Ca* above 0.43 millimolar has relatively little effect until the excess becomes large (A. J. Clark *et al.*, 1928). Segments of *turtle ventricle* are not materially affected by deficiency or excess of Ca (Chu and Sollmann). *Perfused cat heart* shows increased coronary flow when the Ca of the Locke solution is doubled. This is much greater than the slight increase in the height of the contractions, indicating dilatation of the coronary vessels (Mancke, 1930).

Cardiac Vagus.—The presence of Ca is necessary for the inhibitory activity of the vagus (Schiff; Busquet and Pachon, 1909), but apparently not for muscarine (O. Loewi, 1912). However, contradictory results are often obtained. With *perfused mammalian hearts, increase* of Ca to two or three times that of Locke's solution generally lowers the threshold of vagus excitability, but occasionally the effect is reversed. *Decrease* of Ca may raise or lower the excitability (Mandelstamm, 1927). With perfused *turtle* heart, deficiency or absence of Ca in the solution does not interfere with vagus excitability (Brine, 1917). With *frogs,* somewhat smaller concentration of Ca suffices in the presence of K (Hagan and Ormond, 1912). A moderate decrease of Ca increases the excitability of the vagus; excess of Ca diminishes the excitability (Cazzola, 1913). Similar phenomena are observed with the *pelvic and chorda tympani nerves* (O. Loewi, 1912). Increase of Ca also restores the irritability of the vagus when this has been *depressed by Mg* (Auer and Meltzer, 1909). The *vagus center* is stimulated by intravenous injection of calcium chloride, for section of the vagi prevents cardiac slowing on intravenous injection of calcium chloride in dogs (de Nito, 1928).

Blood Vessels.—Hooker, 1911, found that Ca perfusion dilates the vessels of the *frog.* Cow, 1911, found the sensitiveness of *mammalian* arterial rings to epinephrine and pituitary increased by absence of Ca; the reaction to barium was unaffected. *With perfused organs,* Hayashi, 1927, found Ca ions indispensable for vasoconstrictor action by digitalis glycosides, favorable for hydrastinine, indifferent for barium, antagonistic for epinephrine. With *perfused frogs,* deficiency of Ca in the fluid causes the *production of edema;* excess of Ca produces capillary constriction and arrests the flow (H. J. Hamburger, 1922). Hamburger advised a solution containing NaCl 0.6 + $CaCl_2$ (anhydrous) 0.0035 per cent. The *carotid sinus vasomotor reflex* is diminished by hypocalcemia (oxalate injection or parathyroid excision) and promptly restored by the injection of calcium (Heymans *et al.,* 1933).

Circulation-Time Test.—Intravenous injection of 3 to 5 cc. of 10 per cent calcium gluconate or chloride solution causes a sensation of heat which travels with the solution in the blood stream. It is first noted in the mouth, beginning normally ten to seventeen seconds after the injection (S. J. Goldberg, 1936).

Nerve Fibers.—The threshold for electric stimulation is raised by increase of Ca ions and lowered by their decrease, until sequences of impulses are discharged in response to the stimulus (Brink, Sjostrand and Bronk, 1939). If a motor nerve is placed in a decalcifying solution, rhythmic twitchings start in the muscle within five minutes, and increase to tetanus (J. Loeb, 1901).

Calcium Precipitants on Brain.—Direct application of calcium precipitants to the cerebrum stimulates the white matter and increases the excitability of the gray matter to electric stimulation (Maxwell, 1906).

Skeletal Muscle.—Excised frog muscle when immersed in NaCl solution develops rhythmical contractions, which are abolished by the addition of Ca (Sidney Ringer, 1883) and increased by sodium citrate or oxalate, which disionize the calcium. The antagonism is mutual. If the rhythmic contractions do not start in the decalcifying solution, they will generally do so when the muscle is removed to air or oil (J. Loeb, 1901). Calcium also abolishes the rhythmic contractions induced by guanidine, barium or physostigmine, and has some *curare action* (Joseph and Meltzer, 1911). S. W. Kuffler, 1944, claims that calcium deficiency first increases the sensitivity, then blocks the motor end plates, and that calcium excess depresses the electrical excitability of the muscle fiber near the end plates. *Rigor mortis* is hastened by the systemic administration of Ca, delayed by Mg (Meltzer and Auer, 1907). *Isolated fibers* of skeletal muscle shorten to a fourth of their length if their cut surface is exposed to dilute calcium chloride solution for two or three minutes. Naked *protoplasm* in general is clotted or jelled by low concentrations of calcium ions (Heilbrunn, 1940).

Use of Calcium in Convulsions.—The depressant action of calcium suggested its use in *strychnine poisoning,* but Fischer (1904) found it ineffective. Zanda (1902) obtained better results by dural injection, but the effective dose was so large as to be itself dangerous. Januschke and Masslow, 1914, concluded that even large doses of calcium have no direct inhibitory effect on experimental convulsions, whether cerebral, medullary or spinal. The apparently successful results of Januschke, 1913, and presumably those of Yogi, 1912, and other workers, are attributed to delayed absorption of the hypodermic injections of the convulsants, which results from previous calcium treatment. Beutner and Wastl, 1939, reported that injection of calcium chloride, 100 mg. per Kg., reduces materially the incidence of procaine convulsions in guinea pigs, but that calcium gluconate is ineffective. Calcium chloride administration controls the *tetany* arising from *parathyroid deficiency* or other causes (Netter, 1907; W. G. McCallum and Voegtlin, 1908; Kinnicutt, 1909). Goeppert advised 8 to 14 Gm. of calcium chloride daily, in doses of 1.5 to 2 Gm. The administration must be continuous, for spasms reappear if it is discontinued for twelve hours (M. Klotz, 1915). Gruenfelder, 1913, reported that *laryngospasm* and tetany are controlled more promptly by calcium bromide (2 Gm. per day) than by sodium bromide.

Smooth Muscle.—Absence of calcium suppresses the rhythmic contractions, which reappear when Ca is added (Buglia, 1911). Large excess of calcium is also depressant. Slight departures from the ordinary concentrations of the blood or Ringer's solution have little effect. The responses to intermediate changes are complex. Deficiency of calcium income is reported to cause hypotonicity of the colon (E. C. Roberston, 1938). For *excised intestine* of cats, Vanysek, 1914, stated that calcium chloride stimulates the circular and relaxes the longitudinal muscle. Auer and Meltzer, 1909, observed that the intravenous injection of Ca produces a maximal *miosis,* in which the pupil is irresponsive to sympathetic stimulation. The simultaneous exhibition of other drugs shows interesting complex phenomena. The miotic action appears to be due mainly to direct stimulation of the sphincter muscle fibers, and probably also of their nerve endings, supported by diminished irritability of the peripheral sympathetic mechanism. *Spasms of the urinary tract,* bladder, ureters, renal pelvis and calyx are often completely relieved clinically by intravenous injection of 10 cc. of 10 per cent calcium gluconate solution; it fails, however, in some patients, especially if the urine is alkaline or excessively acid (H. R. Trattner and Walzak, 1944). **Ciliary movement** in frog's pharynx is depressed by excess of calcium (S. Ishikawa and Ohzono, 1931).

Gastric secretion of dogs, when increased by histamine or vagus stimulation, is checked by intravenous injection of calcium lactate, 4.3 to 13 mg. per Kg. (R. Grant, 1941).

Effect on Effusions.—R. Chiari and Januschke, 1910 and 1911, reported that the hypodermic injection of Ca prevents the pleural effusion which ordinarily occurs after fatal doses of NaI, diphtheria toxin, thiosinamine, and so forth. It also prevented the inflammatory edema of the conjunctiva after oil of mustard or abrin; and the irritation of the skin by croton oil (Luithlen, 1913). It has been found similarly useful in various skin rashes. Some of these results were contradicted by Levy, 1911 and 1914. H. Gold, 1928, found that calcium chloride injection tends to prevent effusion after pleural injection of copper sulfate, but was unsuccessful against severer irritation. The effect of a dose lasts about a day. Fleischer, Hoyt and L. Loeb, 1909, found that $CaCl_2$, intravenously, decreases the elimination of injected saline fluids, not only by the kidneys, but to a lesser extent also by the intestines. It also causes some depression of intestinal absorption. On the other hand, it increases the tendency to peritoneal and pulmonary transudation. This is only partly due to interference with the kidney function, for the ascitic tendency is exaggerated by Ca even after nephrectomy. Yanagawa, 1916, did not obtain any effect on the *lymph flow;* but his observations were restricted to acute changes.

Mechanism of the Antiedemic Action.—Chiari and Januschke suggest that the Ca has a precipitant effect on the cement substance of the endothelium. Deltjen (1904) observed that small traces of calcium, strontium, barium and magnesium lessen the solvent action of distilled water on cells. Herbst found that sea urchin ova swell when Ca is removed, and shrink when it is added. Osterhout, 1911 and 1912, showed that $CaCl_2$ prevents the entrance of NaCl into spirogyra filaments, and that it renders the plasma membrane of kelp (laminaria) impermeable. Pfeffer, 1877, stated that calcium phosphate forms semipermeable membranes. These were investigated in further detail by Meigs, 1915. The changes in the appearance of fluorescein in the anterior chamber of the eye also indicate decreased permeability (G. Rosenow, 1916). *Phagocytosis* may play a part. H. J. Hamburger, 1910, found that therapeutic quantities hypodermically or by mouth, increase the ameboid movements of the leukocytes, and therefore chemotaxis and phagocytosis. This holds true for the leukocytes of rabbits as well as horses (de Haan, 1918); for bacteria as well as carbon. It requires the presence of serum, and the favorable concentration has a narrow range, which varies with conditions and for different organisms (Redden, 1918). On the other hand, Ikeda, 1916, reported that the migration of leukocytes from inflamed frog's mesentery is inhibited by calcium chloride.

Use of Calcium in Skin Rashes, Catarrhs, and Other Conditions.—Wright, 1896, claimed that the administration of calcium chloride tends to prevent the occurrence of serum rashes. Netter, 1907, also believed it useful in urticaria, acute edema, frost bite and pruritus. Other similar conditions said to be relieved by Ca are boils, erythema, lichen planus, hemoglobinuria, and so forth (Luff, 1909); hay fever and iodide coryza (Chiari and Januschke, 1911; Emmerich and Loew, 1915); asthma (Kayser, 1912, 1914). It often fails, even when continued for long periods, and the evidence for its value is not convincing. Large doses must be administered for some time, and even then the clinical benefits are uncertain. The susceptibility to experimental wheals (codeine) does not appear to be influenced by the Ca level of the plasma (Pilcher). Strong solution of $CaCl_2$ (10 per cent), applied to the scarified skin, raises an urticarial wheal (Pilcher and Sollmann, 1916).

Effects of Various Conditions on Skin Reactions.—Luithlen, 1911 to 1913, studying the reaction of the skin of cats to croton oil, found that this may be modified by Ca and oxalates; by different diets (suggesting that eczema may be a constitutional exaggeration of the reaction of the skin to normal irritation); and by the injection of serum, soluble starch and even mineral colloids, *i. e.*, silica.

Calcium in Blood Coagulation.—Ca is necessary for the action of thrombokinase on thrombogen (or for the conversion of prothrombin into thrombin: Howell, 1914) and hence for the coagulation of the blood. The coagulation of shed blood is prevented by the addition of 0.1 per cent of a soluble oxalate, or 0.4 per cent of a citrate or fluoride. The latter, however, also acts otherwise than on the calcium. Strontium and barium have the same effect as calcium, in a less degree (Ringer and Sainsbury, 1890).

The addition of calcium to plasma to a certain point increases its coagulability; an *excess of calcium* interferes with coagulation or inhibits it completely. It can then be restored by the addition of citrate (von Zarday, 1933). The *amount of oxalate or fluoride* required to prevent clotting is three or four times the stoichiometric equivalent of the calcium present in the blood (Thompson and Collip, 1932), and it appears necessary to have an excess of the calcium immobilizer to complete the disionization. *If thrombin is decalcified* by citrate or oxalate soon after its formation, it fails to clot fibrinogen solution; but if the thrombin has first aged for several hours, then decalcification does not prevent clotting; so that there appears to be a "calcium-containing intermediate," which changes to stable thrombin (J. H. Ferguson, 1937). With *hirudin plasma* the coagulation is further delayed by the addition of calcium (Hess, 1915).

Historical.—The influence of calcium on coagulation was not recognized till 1879 (Hammarsten and others); its indispensability was first shown by Arthus and Pagès, 1890. The inhibition of coagulation by plant juices, which is due to disionization of calcium, was described by Archibald Pitcairn, 1717 (Sollmann and von Oettingen, 1926).

Calcium administration has little if any effect on coagulation time, since the normal calcium concentration of the plasma is close to optimal.

Estimations of the coagulation time after administration of Ca have given contradictory results, owing partly to differences of technic, partly to the time when the observations were made. The experiments of Velden, 1913, indicate that the coagulability is indeed increased for a short time. This increase is also produced by equal quantities of NaCl, and is probably due to a local action on the alimentary canal. It does not last beyond twenty or thirty minutes and would therefore be useless. An hour after *intravenous injection of calcium chloride,* Kormos, 1933, found the plasma level of calcium, thrombin and fibrogen increased, and also higher sedimentation rates; the bleeding time, coagulation time and thrombocyte count were decreased. The changes began to regress in three hours and were gone in twenty-four hours. Intramuscular injection produced the same changes in less degree.

Calcium as hemostatic was tried clinically in operations usually attended with considerable or persistent hemorrhage, as in obstructed jaundice (Lee and Vincent, 1915), and in aneurysm purpura (Russel, 1907) and hemophilia (Wright, 1893); but since the calcium level is normal in these conditions, and therefore optimal, it is doubtful whether any good is accomplished. Indeed, the addition of calcium to hemophilic blood *in vitro* delays rather than hastens coagulation (Hess, 1915).

Coagulation of Milk.—Ca is necessary for the precipitation of the casinogen as casein. Its place may be taken by Sr and Ba (Harris, 1896).

Acid: Base Balance.—When calcium chloride is administered by mouth, a part reacts in the intestine with phosphate and carbonate to form insoluble basic salts which are excreted with the feces, leaving the unbalanced chloride ion to be absorbed, and thereby increasing the proportion of fixed acid in the body and the acidity of the urine (Haldane *et al.*, 1923). This acidity tends to dissolve and mobilize the bone calcium, so that the prolonged administration of large doses of calcium chloride to animals may actually produce rarefaction of bony tissue (Etienne, 1912).

Calcium lactate and gluconate have less of this acidifying effect, as their anions form feeble acids. *Calcium carbonate* is alkalizing. *Intravenous injection* of calcium is less effective, as only the part excreted into the intestines participates in the reactions. When calcium chloride is *added to serum in vitro*, it decreases the bicarbonate content by forming $CaCO_3$. This is not precipitated in the presence of the protein colloids, but is removed from the aqueous phase (Lipschitz, 1939). For *acidification of the urine*, 1 to 3 Gm. (15 to 45 grains) of calcium chloride are administered four times daily with meals. It may be prescribed as a 45 per cent solution, to be freely diluted. It is used as a diuretic, especially in cardiac edema if digitalis alone does not suffice (Goldring, 1929). Calcium lactate may be effective.

The *urine flow* tends to be increased, in normal individuals, presumably mainly by the acidosis. In perfusion of excised kidney, calcium decreases the vein and ureter flow (Sollmann), but this involves unphysiological concentrations. *In nephritis* (particularly glomerular), large doses of calcium chloride by mouth sometimes cause marked diuresis, but may be ineffective (Keith and Barrier, 1924). The diuresis may outlast the administration (Blum), so that it may be due to absorption of the nephritic edema, rather than to a renal action. Duenner, 1916, found that intravenous injection of calcium into rabbits converted subacute uranium nephritis into the acute form. In human nephritis, Jacoby and Eisner, 1913, found that calcium administration decreased the excretion of chloride, iodide and nitrogen. Abe, 1913, claimed that it prevents the increase of urate excretion by cinchophen. Hamburger found that the sugar retention of frog kidneys was conditioned on a narrow zone of calcium concentration.

Calcium Carbonate in Digestive Tract.—Precipitated calcium carbonate is used as an *abrasive tooth powder*. It is a sparingly soluble alkali, which neutralizes the gastric juice without rendering it actively alkaline. This is used against *hyperchlorhydria*, and to increase the base:acid balance of the body.

The *pH of saturated $CaCO_3$ solution* is 8.8; of $Ca(HCO_3)_2$, 5.98 to 6.2 (J. W. Williams and Chucka, 1927). *Calcium phosphate* also buffers gastric hyperacidity, but has little or no effect on the acid-base balance (none with basic phosphate, slight increase with acid phosphate). *Calcium chloride intravenously* (10 cc. of 10 per cent for man) increases the gastric acidity. This is inhibited by epinephrine, not by atropine (Petrovic, 1926).

Diarrhea tends to be relieved by calcium carbonate or calcium phosphate, 1 Gm. every two hours. They act chiefly as protective powders, analogous to bismuth, partly as antacid, and possibly by diminishing permeability. If prescribed in suspension, the Prepared Chalk is preferred, as it is more colloidal.

Intestinal Flora.—Rats on salt-poor diet develop diarrhea by the displacement of their normal intestinal flora, predominantly B. acidophilus, by the coli, proteus and streptococcus groups. The addition of Ca and PO_4 tends to restore the normal flora (Eppright, Valley and Smith, 1937).

Saline Cathartics.—Chiari, 1910, called attention to the fact that all the cathartic ions are antagonistic to Ca; this may explain their action, at least partly.

Oral Administration for Systemic Action.—Milk deserves preference for securing adequate calcium income; a pint furnishes 0.45 Gm. of Ca. If it is not feasible, calcium phosphate may take its place. Calcium carbonate and phosphate are absorbed almost as well as any of the calcium salts, since they are largely converted into soluble salts in the digestive tract (O. Loew, 1914). They should therefore serve as well for oral administration as the water-soluble chloride, lactate or gluconate, but as these happened to form the starting point of the modern calcium therapy, they are generally prescribed. The chloride is less costly, but its taste is more disagreeable. Fantus recommends syrup of acacia to disguise the taste. The single *oral dose* of the chloride is 0.5 to 1 Gm., 8 to 15 grains, in solution, with meals. *Calcium gluconate,* which contains 9.3 per cent of Ca, has the advantage of being practically tasteless by mouth, and nonirritant by hypodermic or intramuscular injection; its intravenous toxicity is about a fourth that of calcium chloride (Rothlin, 1927). The adult dose is 5 Gm. three times daily, by mouth; 1 Gm. on alternate days intramuscularly. Its solubility in water at room temperature is about 3 per cent.

Hypodermic administration has no material advantage. The gluconate or lactate is preferred to the more irritant chloride; at least, the chloride should not be used in concentrations above 1 or 2 per cent, or there will be indurations or sloughing (Wright, 1896; Seelig, 1925). The local injection of calcium chloride also breaks down the local resistance against bacterial infection, at the site of injection ("kataphylaxis"). This has been used to induce experimental infections (Bullock and Cramer, 1919; abscesses, Rossides, 1926). The concentration of the lactate should not exceed 5 per cent since stronger solutions solidify (Hugenholtz, 1915). The *hypodermic dose* of the lactate is 0.5 to 2 Gm. in 20 to 50 cc. of water. *Intravenous injections* are employed in spasmodic conditions; 2 to 4 Gm. of the chloride or lactate in a liter of normal saline, injected slowly. The chloride should not be injected intravenously in concentrations above 1 per cent (Seelig, 1925), lest the escape of the solution around the needle cause sloughing. The gluconate may be injected as 10 cc. of 10 per cent. *Calcium should not be injected into digitalized patients.*

The daily dose against serum rash is 0.75 to 1 Gm., beginning on the day of the antitoxin injection, and continuing for three days after the last injection (Netter, 1909). Against hay fever, hemorrhage, and so forth, 1 to 3 Gm. are given daily, commencing as early as possible and continuing for several weeks. This continued use does not seem to cause harm (Emmerich and Loew, 1913, 1915). The lactate may be given in double this dosage. Hypodermic and especially intravenous administration appear inadvisable.

PREPARATIONS.—***Precipitated Calcium Carbonate,** U.S.P. (Precipitated Chalk), $CaCO_3$, is a fine white powder, without odor or taste. Practically insol. in water; decomposed by acids. Dose, 1 Gm., 15 grains, as powder. This neutralizes 0.730 Gm. absolute HCl. Larger doses are harmless. ***Prepared Chalk,** U.S.P. (Creta Praeparata; Drop Chalk), is native *Calcium Carbonate* freed from most of its impurities by elutriation. A very fine, amorphous powder, often formed into cones.

Chalk Mixture, U.S.P. (Mistura Cretae), contains 6 per cent of Prepared Chalk, suspended in water with Bentonite clay, and flavored with saccharin and cinnamon. It must be recently prepared. Dose, 15 cc., 4 drachms. *Calcium Phosphate, Precipitated,* U.S.P. (Tribasic Calcium Phosphate), $Ca_3(PO_4)_2$, is practically insol. in water. Dose, 1 Gm., 15 grains. *Dibasic Calcium Phosphate,* U.S.P., $CaHPO_4.H_2O$, almost insoluble in water. Dose, 1 Gm. *Calcium Hydorxide Solution,* U.S.P. (Liquor Calcis, Lime Water), contains about 0.15 per cent of $Ca(OH)_2$. A clear, colorless liquid of alkaline taste. Dose, 15 cc., 4 drachms.

***Calcium Chloride,** U.S.P. (not to be confused with Chlorinated Lime, miscalled "Chloride of Lime"), $CaCl_2.2H_2O$, contains about 78 per cent of $CaCl_2$; odorless; sharp saline taste. Very deliquescent, and should therefore not be dispensed in powders, but as solution. Freely sol. in water (1:1.2); also in alc. (1:10). *Incompatible* with carbonates, phosphates and sulfates. Dose, by mouth, 0.5 to 2 Gm., 8 to 30 grains, diluted; intravenous, 1 Gm. ***Calcium Gluconate,** U.S.P., $[CH_2OH(CHOH)_4.COO]_2Ca.H_2O$, yielding about 9 per cent of Ca. A white crystalline or granular powder; odorless; tasteless; stable in air. Slowly sol. in water (1:30) with practically neutral reaction. More palatable than the chloride; for hypodermic or intramuscular use is nonirritant. Dose, oral, 5 Gm.; intravenous, 1 Gm. *Calcium Gluconate Injection,* U.S.P., a watery solution. May be stabilized by the addition of other calcium salts up to 5 per cent of the gluconate. Usually available in ampuls of 1 Gm. in 10 cc. *Calcium Levulinate* (dihydrated), N.N.R.; properties similar to those of gluconate; virtually nonirritant. *Calcium Lactate,* $Ca(C_3H_5O_3)_2.5H_2O$, U.S.P., occurs as white, granular, odorless, tasteless powder. Sol. in water (1:20), but very slightly sol. in alc. Dose, 1 to 4 Gm., 15 to 60 grains.

PARATHYROID HORMONE

The hormone of the parathyroid glands, "*parathormone,*" which has not been isolated in pure form, regulates the Ca and PO_4 metabolism. Its deficiency, as by excision of the glands, lowers the Ca level of the plasma and tissues, causing tetany; its injection increases the Ca level and produces sedation, muscular and nervous. The symptoms resulting from excision are relieved by increasing the Ca level, by the injection of calcium salts or of parathyroid extract or by the administration of vitamin D; the chief difference is in the promptness and duration of the relief. The parathyroid glands are not essential to life, if the calcium level is kept up, as by vitamin D. However, while both agents raise the calcium level of the blood, the mechanism of their action is different. Parathyroid hormone lowers the PO_4 level and withdraws calcium from trabecular bone; vitamin D raises the plasma level of both Ca and PO_4, chiefly by better absorption from the intestines. The significant changes in the plasma level and urinary excretion of calcium and phosphate are shown in the following tabulation:

EFFECT OF PARATHYROID

	Administration	*Deficiency*
Renal PO_4 threshold	lowered	raised
Urinary PO_4 excretion	increased	decreased
Serum PO_4 level	lowered	slight absolute rise; marked increase of PO_4:Ca
Serum Ca leve	rises to double normal	falls to ½ or ⅓ normal
Urinary Ca exclretion	tends to rise	tends to fall

The fecal excretion of both elements is not materially changed.

Administration of parathyroid hormone to rats decreases the retention of *radioactive strontium* in the femur, decreases its fecal excretion, increases its urinary excretion, and produces marked retention of strontium in the kidneys (W. R. Tweedy, 1945).

Historical.—The parathyroid glands were discovered by Sandstroem, 1880, and their physiological importance was pointed out by Gley, 1892. The actions of the parathyroid hormone were placed on a definite quantitative basis by the discovery of Collip, 1925, that the calcium content of blood plasma can be markedly raised by the intravenous injection of purified acidulated aqueous extracts of the parathyroid gland (similar to the extracts prepared by A. M. Hanson, 1923). The literature is reviewed by D. L. Thomson and Collip, 1932; A. M. Hanson, 1935; and Aub, 1935.

Calcium Content of the Plasma.—The removal of the parathyroids from dogs lowers the plasma calcium from the normal (about 10 mg. per 100 cc.) to 8, 5 or even 3 mg., in twenty-four hours to ten days. A single injection of the parathyroid extract restores the calcium level to the normal, and as this is approached, the spasmodic phenomena disappear. The calcium level reaches a maximum in nine to eighteen hours, and then declines to the previous level, in twelve to thirty-six hours. By repeating the injections daily, the calcium can be maintained at the normal level, and the tetany kept completely suppressed. Injection of the extract in normal animals raises the plasma calcium in an entirely similar manner; the rise merely starts from a higher level and therefore passes at once into hypercalcemia. A single dose may raise the calcium to 18 mg.

The rise is gradual, reaching its maximum in twelve to eighteen hours after intramuscular injection. It is more rapid on intravenous injection, reaching its maximum in four to eight hours, but this is only about one-half as high as with intramuscular injection. Oral administration is generally ineffective. The recovery of the calcium level is similarly gradual, the duration depending on the rise. With repeated administrations, the response diminishes gradually and disappears entirely after several months. *With the injections repeated* at intervals of four hours, the calcium level rises to a maximum of about 20 mg. in twenty hours, remains there for some time, then begins to decline, about the thirty-sixth hour, in spite of the continued administration.

Differences in Animals.—*Man and dogs* are especially responsive, and run a similar course in every respect. *Rabbits and rats* give variable results, but do not ordinarily respond with marked hypercalcemia, because their renal and intestinal excretion of calcium keeps up with its mobilization from bone (Pugsley, 1932). *Complete excision of the parathyroids in rats* causes a fall of the calcium level comparable with that in dogs. The level begins to ascend spontaneously in about three months and is practically normal in seven to ten months. The operated rats are two or three times more reactive to parathyroid injection than are normal rats (Tweedy and Chandler, 1929). Reports of different workers vary as to *cats*. The rise of serum calcium on injection of parathormone is faster and higher if the external temperature is below 50° F. (T. J. C. Combes, 1942).

The *phosphate level of the plasma* is also altered by the parathyroid hormone, but not so strikingly. *Administration* of the hormone lowers the PO_4 level until the Ca rises above 14 to 15 mg., when it rises (apparently because the renal threshold rises when above this level).

In deficiency, the PO_4 rises slightly, the P:Ca markedly (Albright, Bauer and Ellsworth, 1929).

Urinary Excretion of Phosphate and Calcium.—*Parathyroid deficiency* strikingly decreases the phosphate excretion. The urinary calcium excretion is slightly decreased. The fecal excretion of both elements may be somewhat increased, but not materially so. The phosphate retention precedes the other changes; as it does not materially raise the PO_4 level of the blood, it may be assumed to be precipitated with calcium (Greenwald and Gross, 1925; Albright and Ellsworth, 1929), presumably in bone. Administration of sodium phosphate prevents the rise of serum calcium by parathormone injection (A. H. Neufeld and Collip, 1942). *Administration of parathyroid hormone* promptly increases urinary phosphate excretion, reaching a maximum in two hours (Albright and Ellsworth, 1929). The Ca excretion also tends to rise, but not so promptly, and, with overdosage, the phosphate excretion may be greater than the corresponding calcium (Greenwald). The fecal excretion again is not materially altered. The *mechanism of the parathyroid action* is not clear. A. H. Neufeld and Collip, 1942, reported that the parathormone injection has no effect when anuria is produced as by clamping the renal vessels, indicating that its action is directly renal; but Selye, 1942, found that the bone changes occur after nephrectomy; and E. P. Monahan and Freeman, 1944, found that the serum calcium level of nephrectomized animals is lowered by removing the parathyroids and that the serum phosphate level is not raised, as would be expected if the parathyroid action were renal. The urinary clearance of injected sodium phosphate of normal animals also is not altered either by injection or deficiency of parathyroid hormone (M. Fay *et al.*, 1942). It appears, therefore, that the primary action is not on the kidneys, but presumably on the osteoclastic and osteoblastic processes in the bones.

Simultaneous injection of calcium chloride and parathyroid hormone has been cited as an argument for direct stimulation of osteoclastic activity. The plasma calcium shows the prompt peak of the calcium injection, then a remission, and then the gradual parathyroid peak. *Acute liver injury* by phosphorus also obliterates hypercalcemic response, but carbon tetrachloride, hydrazine and benzene do not (D. M. Greenberg, 1935).

With prolonged administration of sublethal doses of parathyroid hormone (10 units per day for dogs) the urinary calcium excretion at first increases enormously, for instance from 0.3 to 39 mg. This is followed by a gradual decline; when the administration is discontinued, the calcium excretion drops sharply below normal. The urinary phosphate rises about 20 per cent, remains high during the administration, and falls below normal in the after-period. Fecal excretion of Ca and P is changed but little during the administration, and drops after suspension (Greenwald and Gross, 1926). *Continued administration to human adults and normal and rickety children* leads to negative calcium balance, by increased urinary excretion, even when the plasma calcium is not raised. The fecal excretion is slightly increased. On low calcium income, the Ca balance becomes more negative, the urinary phosphate excretion rises and the plasma phosphate falls (Albright, Bauer, Ropes and Aub. 1929). The *loss of potency* when injections are continued for several months is not due to exhaustion of the calcium reserves, for ammonium chloride still produces ionized calcium elimination, and viosterol is still effective (Albright *et al.*, 1929).

Calcium Partition in Serum.—The increase on *parathyroid injection* involves first the more diffusible calcium; but the rise of the less diffusible is more prolonged, so that the normal ratio is eventually restored (Moritz, 1926). With *parathyroid deficiency*, the ratio of diffusible and nondiffusible plasma calcium is either unchanged or the nondiffusible is increased. The *calcium level of cerebrospinal fluid*, which is normally about half that of the serum, is but little changed by parathyroid administration, or at least very slowly. Injected calcium also does not pass readily into this fluid.

The *source of the calcium* for the increased plasma level and the increased excretion comes from the food calcium, and beyond this from trabecular bone. The latter may suffice, for evisceration does not diminish the rise of calcium level. None comes from the liver, spleen, pancreas, pituitary, thyroid or central nervous system (C. P. Stewart and Percival, 1927); the kidneys may show deposits of calcium around and into the tubules (Chown, Lee and Teal, 1936).

The *bone changes with continued parathyroid administration*, as seen in young dogs, consist in marked resorption of bone, both spongy and cortical, with *osteofibrosis*. Guinea pigs show bone resorption even after a single dose (Jaffe and Bodansky, 1930). Analogous changes occur in cats, rabbits and rats. The bone fractures more readily, the trabeculae are fewer, the ash is decreased, but its calcium percentage is higher (Lambie, Kermack and Harvey, 1929; Bauer, Aub and Albright, 1929).

Prolonged parathyroid deficiency causes the *teeth* of rats to become opaque, brittle, distorted, with general disorganization of the enamel, and with exostoses of the alveolar bone (J. Erdheim, 1911). The *bones* are low in ash, Ca and P, relatively high in Mg. Muscles and viscera do not have increased calcium. Cataracts are common. The *teeth and jawbones* of rats are also affected by continued administration, similarly to faulty Ca:PO_4 ratio in the diet, or to viosterol deficiency. The pulpar surface shows congestion, degeneration of the odontoblasts, fibrosis and necrosis; with poor calcification of the dentin and enamel (Backberg and Berke, 1934). Matured teeth, in man, do not show resorption, although the surrounding bone is markedly resorbed (K. H. Thoma, 1933; Albright, Aub and Bauer, 1934).

Clinical osteitis fibrosa cystica is attributable to progressive decalcification by hyperparathyroidism, generally from adenoma (F. Mandl, 1927). Osteitis deformans has no connection with parathyroid function; osteomalacia proper is due to deficiency of calcium income and vitamin D.

Parathyroid Administration on Other Salts.—The plasma chloride is markedly increased. The alkali reserve is somewhat lowered. The total ash and the magnesium content of living tissue are lowered by continued administration, but the magnesium as well as calcium percentage of the ash is raised (Coppo and Pisa, 1935).

The **symptoms following total excision of the parathyroid glands** are most striking when both glands are removed at one operation, in dogs, but they are entirely similar in man and are due solely to the hypocalcemia. They begin with refusal of food and water; then restlessness and hyperexcitability; then persistent emesis, leading to alkalosis; *hyperexcitability of the peripheral motor nerves to electric stimulation*, which is probably the earliest detectable sign: pruritus; diarrhea, often bloody, attributed to hyperexcitability of the innervation of the gastro-intestinal tract with tendency to acute digestive uclers; fibrillary twitchings of the skeletal muscles, saltations, *tetany*, then convulsions, initiated by clonic and tonic contractions. This sequence may terminate in death, after about six major convulsions, either from respiratory spasm or from exhaustion; or the convulsions may become milder, with gradual recovery.

The *ammonium content* of the blood is increased by depressed functionation of the liver (Carlson and Jacobson, 1910). *Guanidine*, histamine and similar *toxic bases* appear in the urine (W. F. Koch, 1913). D. M. Paton *et al.*, 1917, suggested that the parathyroids regulate guanidine metabolism and so control muscular tone.

The *carbohydrate tolerance* is lowered by excision of the parathyroids (Underhill and Hilsditch, 1909).

Destruction of the parathyroids also increases the *vasoconstrictor response* to nicotine, epinephrine and pituitary, involving therefore the most peripheral vasomotor mechanism. This effect is counteracted by calcium (Hoskins and Wheelon, 1914).

Removal of the parathyroids from rats increases their *appetite for calcium*, so that they drink suitable calcium solutions in preference to water. This is also used for the bio-assay of substances that affect the blood calcium (C. P. Richter and Birmingham, 1941).

Variations of susceptibility are marked, according to the amount of accessory parathyroid tissue, and other factors. The mortality of untreated dogs is 95 to 100 per cent; cats, 50 to 80 per cent; rabbits, 13 to 33 per cent (Dragstedt); rats generally survive and are therefore used to study the prolonged course. Rabbits die if all accessory parathyroid tissue is removed. Cats generally show only depressive symptoms. Old animals are less susceptible than young. Pregnancy and rickets, and calcium-poor or phosphate-rich diet accelerate tetany and death. Carnivora are most susceptible, especially when fed on meat alone. Accessory parathyroid tissue is frequent, especially in cats, mainly as inclusions in the thymus gland. It hypertrophies when the chief glands are excised, so that the animals which escape early death generally return to normal. Two stage removal is therefore much less fatal than one stage. This hypertrophy is not the sole element in the recovery, however, for accessory tissue has been demonstrated in only 10 per cent of the rats which survive, although their serum calcium falls low (5 to 8 mg. per cent) and returns slowly to normal values (in three to nine months).

Phenomena of Overdosage.—When the calcium level of the plasma rises above 15 mg., the phenomena of calcium poisoning develop. Their severity depends not only on the extent, but also on the duration of the calcium rise; a single injection is therefore rarely fatal even if the level reaches 20 or 23 mg.; continued administration would invariably be fatal, even at lower levels, 18 to 23 mg. Uncontrolled administration of parathyroid hormone would therefore be dangerous, but there is no danger under proper conditions; *i. e.*, careful dosage, surveillance of the patient and immediate discontinuance when *warning symptoms* of overdosage appear, namely, vomiting and diarrhea. The acute effects are due primarily to the hypercalcemia, but they become complicated as they progress. The acute effects, in dogs, are usually confined to weakness and apathy, sometimes with vomiting, without significant changes of blood pressure. After about twenty-four hours, when the plasma calcium turns downward, the symptoms become more severe, passing through anorexia, diarrhea, vomiting, extreme lassitude, muscular atony, lethargy and coma, to death. There is marked dehydration, the plasma volume diminishes greatly, the blood viscosity rises correspondingly and hinders the circulation (Collip and Clark, 1925). The urine output is greatly diminished; the urea, the phosphate, and the osmotic pressure of the blood plasma increase. Acidosis develops.

Postmortem examination shows intense capillary hyperemia of the stomach and small intestines, culminating in hemorrhages. The lesions are coextensive with the vagal innervation and appear to be due to vagal hyperexcitability. They may be prevented by atropine or by section of the vagi, although these do not prevent the hypercalcemia (N. B. Taylor, Weld and Sykes, 1933). Hemorrhages occur also in the bone marrow.

The *course* of the parathyroid overdosage differs considerably from that of calcium chloride injection, since this does not produce a sufficiently lasting rise of blood calcium; but similar effects follow if sodium biphosphate is injected with the calcium (Collip, 1926). *Susceptibility to parathyroid intoxication* appears low in many animals, such as cats, rabbits, rats, mice, guinea pigs, and fowl.

Perfusion of frogs with parathyroid hormone is reported to increase the height of *muscular contraction* to 400 per cent. This effect is abolished by inactivation of the hormone by acid or alcohol, and by curare, by degeneration of the nerve endings and by calcium deficiency; but the Ca may be replaced by strontium. The response may be used for bio-assay (Gellhorn, 1935). *Exudate formation*, in response to pleural injection of copper sulfate in dogs, is reported to be diminished when the plasma calcium level is markedly raised by parathyroid hormone (H. Gold, 1928).

Moderate but long-continued overdosage may lead to myasthenia, renal damage, rise of blood phosphate, abnormal deposits of calcium in soft tissues, kidney stones of calcium phosphate, rarefaction of trabecular bone and development of osteitis fibrosa cystica, with increased activity of the osteoclasts and usually also of the osteoblasts. Morris, 1915, described *mental symptoms* in a patient, which he was inclined to attribute to the prolonged administration of large doses of parathyroid gland. *High phosphate diet* is beneficial in clinical hyperparathyroidism, but not completely effective. The serum phosphate rises, but is rapidly excreted; the serum calcium falls, but not so much as might be expected. The urinary calcium excretion is lowered (Albright *et al.*). *Dietary production of parathyroid hypertrophy* is produced in fowl by maize and wheat. It is retarded by feeding calcium, accelerated by sulfuric acid or neutral sulfur (Marine, 1914). E. J. Baumann and Sprinson, 1937, produced parathyroid hypertrophy in rabbits fed on carrots and oats, with a P:Ca ratio of 0.5. The plasma phosphate is low, calcium high. The circulatory parathyroid hormone is increased, the serum phosphatase diminished.

Clinical Tetany.—Excision of the parathyroid glands in man is followed by the same phenomena as in animals. Tetany, more or less painful tonic spasms of the muscles, particularly of the extremities, sometimes associated with parasthesias and fibrillary twitching, may appear between sixteen hours and six days after the operation. It is not conditioned on any fixed calcium level of the plasma; it may be present at 8.7 mg. per cent, or absent at 3.5 mg. Thomson and Collip believe that the calcium deficiency causes only twitching, and that the tetany proper and the convulsions are caused by the alkalosis which develops from the hyperpnea when the muscular tremors and the calcium deficiency increase the heat production. Raising the temperature brings on tetany in parathyroidectomized dogs, and cooling diminishes the convulsions (W. R. Bryan and Garrey, 1931).

In harmony with this, the convulsions may be arrested by producing acidosis, by ammonium chloride (T. E. Boyd, Austin and Ducey, 1926) or other acidic agents, by inhaling carbon dioxide (Swingle, Wenner and Stanley, 1928), by uranium nephritic acidosis (Swingle, 1928), and indeed by the acid produced by the convulsions themselves; and of course also by calcium chloride administration which acts both as acid and as calcium; and finally by increasing the calcium-ion concentration by parathyroid hormone or viosterol. This conception *unifies the causes of tetany* (R. Ellsworth, 1933) as alkalosis (1) directly by alkali injection, including alkaline phosphate (Binger, 1917) and the excessive vomiting of gastric tetany; and (2) secondary to calcium deficiency and hyperpnea, in parathyroid deficiency, low-calcium rickets, citrate or oxalate injection (J. Loeb, 1901) and calcium loss by the persistent diarrhea of cholera. In *infantile tetany* the spasmodic symptoms are paralleled by a corresponding fall of the plasma calcium to a mean of about 5 mg. per 100 cc. (Howland and Marriott, 1917). The concentration of the phosphate in the plasma is approximately normal, but the excretion of phosphate in the urine is diminished.

Guanidine tetany resembles parathyroid tetany symptomatically, and increase of the guanidine content of the blood and urine was reported, but the analytical methods proved to be untrustworthy (R. H. Major, Orr and Weber, 1927; Greenwald). Watanabe, 1918, reported that the blood serum contains about the normal amount of calcium, but that the phosphate content is markedly increased. The claim that guanidine lowers the calcium level is not supported by conclusive evidence (G. Bayer, 1932). The blood pressure is generally lowered in parathyroid tetany, and raised with guanidine (Stoland and Bryant, 1926).

Treatment of Parathyroid Deficiency.—Under the stimulus of parathyroid deficiency the accessory parathyroid tissue hypertrophies, and generally becomes quite or nearly adequate after a few weeks. Treatment is indicated to diminish the symptoms during the interim. It comprises the injection of calcium gluconate for immediate relief, which is then sustained for several weeks by parathyroid administration, with abundant calcium income. Viosterol is used if longer treatment is necessary (review, Aub, 1935). Dihydrotachysterol permits material simplification (Albright, 1939). The same treatment is also effective in other tetanies (infantile, gastric) that involve calcium deficiency. Parathyroid therapy is not effective against other spasmodic conditions.

For *immediate relief, calcium salts* may be injected intravenously, preferably the gluconate, 0.15 cc. of 20 per cent per Kg., taking at least four minutes for the injection. A few minutes later, the same quantity of gluconate may be injected intramuscularly (A. L. Lieberman, 1931). The relief is dramatic and may persist over two hours, and the injection may be repeated if the tetany recurs. It is advisable, however, to continue the therapy with *injection of parathyroid hormone*, the full effect of which has a latent period of four hours (although intravenous injection may relieve the tetany in half an hour), but persists for twenty hours after a single injection. A more even effect is obtained, more economically, by administering it twice daily. The dosage and duration must be controlled by frequent determinations of the plasma calcium and phosphate, so that the calcium does not rise above 12 to 13 mg. per 100 cc., for 14 mg. produces hypercalcemic symptoms, loss of appetite, nausea and fatigue. The lower limit is estimated by the continuance or recurrence of tetany, since the individual susceptibility varies. The response to parathyroid injection diminishes gradually and is completely lost after several months. The cause is not understood, as the response to the injection of calcium, to acidosis and to viosterol persists. It is therefore advisable, also for economy, to supplement the hormone with *viosterol* at once, and to omit the hormone injections after two or three weeks, when they would be less effective and less needed. Several days of viosterol administration are required to develop the maximal effect, but it persists for at least two weeks after the administration is discontinued, and can be maintained indefinitely. Even young puppies and pregnant dogs get along without parathyroids if adequate vitamin D is administered (Kozelka, Hart and Bohstedt, 1933). *Dihydrotachysterol*, one of the photochemical derivatives of ergosterol, developed by Holz, is reported especially effective. It is marketed in oil solution, 5 mg. per cubic centimeter, and is administered orally, generally 3 cc. per day until calcium appears in the urine by the Sulkowitch test, and then kept at a maintenance level of about 1 cc. three to five times per week (F. Albright, 1939; Albright, Bloomberg *et al.*, 1938). The *calcium intake* should be liberal during the hormone or viosterol administration, else it would need to be drawn from the bones. The phosphate income should be low. A meat diet is said to be beneficial, perhaps by combating alkalosis; also lactose, perhaps by facilitating calcium absorption and lowering the blood phosphate. Calcium lactate, orally, 1.8 to 4.4 mg. per Kg. per day, prevents the parathyroid tetany in dogs; cow's milk does not; strontium lactate does, perhaps by binding phosphate in the intestines (L. R. Dragstedt and Sudan, 1926). Parathyroidectomized rats exhibit a greatly increased *appetite for calcium* (as lactate or gluconate); their appetite for NaCl, KCl, Na_2HPO_4, NaI or $(NH_4)_2SO_4$ is not greatly changed (J. F. Eckert, 1938).

Other Spasmodic Conditions.—Parathyroid administration and injections have been tried against paralysis agitans (Berkeley, 1909), chorea and eclampsia, apparently without success, for these conditions do not show calcium deficiency. This applies also to gastric tetany, excessive pulmonary ventilation, and other forms of alkalosis. The spasms could probably be allayed by increasing the calcium above the normal, but this would also develop the dangerous effects of hypercalcemia.

Interrelation with Thymus.—Uhlenhuth, 1918, found that mammalian thymus produces convulsions when fed to the larvae of salamanders. This occurs only before their parathyroids have developed. Apparently, thymus contains tetanic poisons, which are antagonized by the parathyroids. Calcium and magnesium also check the thymus convulsions, but much less perfectly.

Other therapeutic uses of parathyroid hormone have been sought, both for the increased calcium level of the plasma, and for the decalcification of bone and other calcium deposits, but with little success (Aub, 1935).

Increasing the plasma calcium level is of little value for healing fractures. Some good results have been reported in persistent edemas, nephritis and cardiac, but they are not convincing; still less convincing are the results in asthma, vasomotor rhinitis, hemorrhage and jaundice. *In experimental oxalate and fluoride* poisoning, of mice, the results are excellent, so that the fluoride toxicity may be used for the bio-assay of parathyroid hormone (Kochmann, 1934). *Decalcification* of various tissues, calcified glands and arteries, myositis ossificans, otosclerosis, and the like, is not successful, as the mobilization of calcium occurs from the organized spongy bone, and not from abnormal deposits.

Removal of abnormal metals stored in the bone trabeculae may be accomplished with parathyroid hormone; for instance, lead (D. Hunter and Aub, 1927), radium, thorium and polonium; but it is not so easily managed clinically as are the acid-producing salts, such as ammonium chloride.

Parathyroid Injection, U.S.P. (Solution of Parathyroid, Parathyroid Extract), is a sterile, watery solution of the calcium-raising principles of fresh parathyroid gland, adjusted by bio-assay so that 1 cc. represents no less than 100 U.S.P. units, each unit being a hundredth of the amount required to raise the calcium content of 100 cc. of the blood serum of normal dogs (of 8 to 16 Kg.) by 1 mg. within sixteen to eighteen hours after subcutaneous administration. The detailed directions of the U.S.P. must be followed. Available in ampuls of 100 units in 1 cc. Average dose, 25 units intramuscularly. The *dosage* should be adjusted according to the effects. The usual range is 10 to 25 units per day, or on alternate days; 10 units in infantile tetany; injected hypodermically, intramuscularly or intravenously, often in fractionated doses. As much as 100 units has been injected in an hour, but this is not advisable, and could not be continued. The extract is somewhat effective by mouth but the absorption is uncertain and difficult to control, and the hypodermic, intramuscular or intravenous injections of the purified extracts are vastly superior.

VITAMIN D, VIOSTEROL, IRRADIATED ERGOSTEROL

Vitamin D is a general name applied to sterols concerned with the proper utilization of calcium and phosphate and the orderly calcification of bone. Their deficiency results in the development of rickets. Vitamin D occurs naturally in foods, especially in egg yolk, milk and in the liver fat of marine fishes, such as cod liver oil. The antirachitic action of sunlight and ultraviolet rays is attributable to the activation of sterols of the skin (A. F. Hess *et al.*, 1925). Ultraviolet therapy is reviewed by E. M. Luce-Clausen, 1938. A series of substances having these properties are obtained from ergosterol by ultraviolet irradiation and by other physicochemical processes. These constitute "Viosterol." Some have been isolated in pure crystalline form. Analogous products of similar properties have been prepared from 7-dehydrocholesterol, and these are probably the forms which exist naturally in the body and in cod liver oil. The relative potency of different products varies for different animals. A "rat unit" of cod liver oil is somewhat more effective against human rickets and especially against the leg weakness of chicks than a rat unit of viosterol (Bills, Massengale and Imboden, 1934). Vitamin D is *stable*, differing in this respect from vitamin A, with which it is associated in cod liver oil. It resists prolonged heating at 100° C., and keeps indefinitely in cold storage.

Historical.—After the existence of antirachitic properties in cod liver oil had been established (by E. Mellanby, 1919), McCollum, Simmons *et al.*, 1922, showed that this vitamin "D" is distinct from the growth vitamin A. Later work confirmed that the "D" does not protect against xerophthalmia and other phenomena of "A" deficiency (Wilkes *et al.*, 1929). About the same time, Huldschinsky, 1919, established analogous antirachitic effects on exposing patients to sunlight or artificial ultraviolet rays. A. F. Hess and H. Steenbock, 1924, independently and almost simultaneously discovered that antirachitic properties can be conferred on many foods and oils, which are not in themselves antirachitic, by short exposure to the ultraviolet rays of the same wave length, about 310 μ, which is effective directly on patients. Starting with the observation that ordinary cholesterol is rendered potently antirachitic by such irradiation, Hess and Weinstock, 1925, showed that this is associated with definite changes in the absorption spectrum of the solution, and that excessive exposure produces further changes in the absorption and destroys the activity.

The *vitamin D content of natural food* is not sufficient for growing children, unless it is supplemented by considerable exposure of the skin to ultraviolet radiation, sunlight or artificial. About the only foods which contain significant but small amounts are milk, liver and egg yolk. Vegetables and vegetable oils contain little; the earlier claims were based on faulty methods (J. Coffin, 1935).

Egg yolk is a good source of vitamin D, so that two yolks a day may cure rickets; but the content is variable. Their activity is not destroyed by hard-boiling, nor by six months of cold storage. *Milk and butter*, which are a good source of vitamin A, contain relatively little D. There is considerable seasonal difference, depending on the rations more than on the sunlight exposure of the cows. It may be increased to sixteen times by feeding irradiated yeast. It is decreased by sterilization or commercial evaporation of the milk (review, Clouse, 1933)

Cod liver oil and the liver fat of other fishes are rich in vitamin D aswell as in A, in varying proportions. Oils from individual fish may differ a thousand times in potency, and the two vitamins do not go parallel (A. F. Hess, Bills and Honeywell, 1929). The body oil of fish is also potent. Fish liver oils contain several D vitamins, distinguished by their relative potency on rats and chicks (Bills, Massengale *et al.*, 1937). All are sterols and therefore pass into the nonsaponifiable lipoid fraction (as does also vitamin A). Such *concentrates* may be used therapeutically, avoiding the excess fat of the oils.

Antirachitic Sterol Derivatives.—At least ten exist, and five of these are well understood. The most important are activation products of ergosterol and of 7-dehydrocholesterol. Most of the others are mainly of theoretical interest. The crystallized "Calciferol" ("D_2") is purified activated ergosterol. It is the active component of viosterol, of irradiated vegetable foods and of "yeast milk," the milk of cattle fed with irradiated yeast. Most of the other antirachitic agents are formed from 7-dehydrocholesterol, the provitamin associated with animal cholesterol. It is the agent activated in the skin by ultraviolet radiation, and the active agent of fish oil, of egg yolk and of directly irradiated milk. At least two forms occur in fish oils, and it is not known whether these are identical with any of those produced artificially (Bills, 1938).

Structural Relations.—The sterols are phenanthrene derivatives, with a "*cholane*" nucleus. This series also includes the bile acids; toad poisons (bufotalin); the estrogenic and androgenic hormones and progesterone; morphine and its derivatives; the carcinogenic compounds; and the aglucones of the digitalis series (Lundgren, 1935; Bills, 1935).

Irradiation Products of Ergosterol.—*Ergosterol* was originally obtained from ergot, but it is widely distributed in plants. At present it is prepared almost exclusively from yeast. Small quantities are present in many vegetable foods. It is insoluble in water, sparingly soluble in oils, freely soluble in most organic solvents. It is levorotatory, unstable, highly unsaturated, with three double bonds (Bills, Honeywell and Cox, 1928). It has a strong absorption band in the ultraviolet spectrum, with three maxima between 260 and 293.5. This disappears with irradiation, and a new band is formed between 240 and 248.

Activation of Ergosterol.—Ergosterol has no antirachitic effects until it is irradiated by specific ultraviolet rays, or by other means which cause an intramolecular rearrangement, involving a shift in the position of a double bond, the atoms remaining the same, $C_{28}H_{43}$-OH. The change is initiated by any wave lengths which are absorbed by the ergosterol (Bills, 1938). These produce progressive changes, as revealed by successive alterations in the spectrum, as well as by successive inintensification and destruction of the antirachitic properties (Hess and Weinstock, 1925; T. A. Webster and Bourdillon, 1929). The means of activation, including electron bombardment, do not alter the nature of the antirachitic substance, but only the rate of production and the amount of by-products. Only some 10 per cent of the ergosterol undergoes activation (Holtz, 1927). The solvent influences the rate of the changes. The pure, dry viosterol soon loses activity; but irradiated foods remain active for at least six months, and oily solutions of viosterol appear to retain their full activity indefinitely.

Time of Irradiation.—The production of the antirachitic substance by irradiation, and its destruction by oxidation go hand in hand. The maximum efficiency is reached in half an hour, so that the activity does not increase by further exposure (Jendrassik and Kemenyffi, 1928; Van Stoek, Dureuil and Hendebert, 1928). Brief exposure is especially important in the *irradiation of food;* even a fraction of a second may suffice in favorable cases, and prolonged treatment develops disagreeable taste and odor and may destroy the A and C vitamins (Clouse, 1933, review). *Wave lengths* of 280 to 302 millimicrons appear most potent for the formation of viosterol; even 230 is effective, but requires much longer. With the quartz mercury lamp, waves shorter than 270 destroy the antirachitic factors (Morton, Heibron and Kamm, 1927). The Sperti patent utilizes longer wave lengths than the ordinary Steenbock patent, claiming a product of higher and more uniform antirachitic activity and lower toxicity (Rider, Sperti *et al.*, 1936). *Activation of ergosterol by other means* has been accomplished with cathode rays, radium emanation, low velocity electrons (McQuarrie *et al.*, 1937), by a clay catalyst and by nitrites (Bills and McDonald, 1926, 1931). These influence the amount of the by-products.

Products of Ergosterol Irradiation.—At least five or six substances are formed in the ordinary irradiation of ergosterol (Windaus, 1930), by overlapping stages as follows:

Ergosterol (cryst.)
↓
Lumisterol (cryst.)
↓
Tachysterol (cryst. derivative)
↓
Calciferol (cryst.) (D_2; Drisdol)
↓
Toxisterol (Substance 248) (has not been obtained pure)

Suprasterol I (cryst.)
Suprasterol II (cryst.)

Calciferol, the crystalline antirachitic fraction, was isolated by Angus *et al.*, 1931, and Windaus, 1931 (Askew *et al.*, 1932), and has been made the international and U.S.P. standard of comparison for viosterol, 1 mg. corresponding to 40,000 units. It is marketed as *Drisdol.* (The substance first named Calciferol, (D_1) Angus *et al.* proved to be a mixture.)

"*Toxisterol,*" called "substance 248" from its single intense absorption band at wave length 248, has toxic and calcifying properties greatly disproportionate to the antirachitic action. It is formed most freely when an alcoholic solution is irradiated, and may be absent if ethereal solution is used. It has not been isolated (Bills, 1938).

Activated 7-dehydrocholesterol.—Cholesterol cannot easily be activated directly, but must first be converted into 7-dehydrocholesterol (J. Waddell, 1934). This is found along with cholesterol in nature and has been synthesized, and highly active antirachitic properties have been obtained by the irradiation of this (D_3), as well as the natural product (F. Schenck, 1937). The activated preparation appears to be similar to the vitamin D of fish oil. A water-soluble antirachitic derivative of this has also been announced.

E. M. Koch and Koch, 1935, 1936, obtained antirachitic preparations by the radiation of certain natural cholesterols, *f. i.*, of the spinal cord, which they attributed to derivatives other than 7-dehydrocholsterol; 22-dehydrocholesterol has also been activated and termed D_4.

The *relative antirachitic activity of vitamin D for different animals* shows marked differences between activated-ergosterol and activated 7-dehydrocholesterol, the rat unit of the cholesterol-derived vitamin (including that of fish oil) being fifteen to twenty times more potent on chicks than the rat unit of activated ergosterol (A. F. Hess, Weinstock and Rivkin, 1929; J. Waddell, 1934). For human rickets, N. Morris and Stevenson, 1939, found no significant difference in the clinical potency of D_2 and D_3. Gerstenberger *et al.*, 1940, reports D_3 more potent than D_2 in treating rachitic monkeys.

The **absorption of viosterol** apparently requires the presence of *bile* in the intestines. Exclusion of the bile from the intestinal tract of dogs results in osteoporosis (Hawkins *et al.*, 1938); and none of the effects, toxic or therapeutic, of viosterol or vitamin D occur in dogs with biliary fistula until bile is fed (or desoxycholic acid, with rats; J. D. Graves and Schmidt, 1933) or until viosterol is injected intravenously (N. B. Taylor and Weld, 1932). The bile of normal animals is itself antirachitic, indicating that vitamin D is also *excreted in the bile.* The reabsorption of this probably explains why hypercalcemia may outlast the administration, often after a single dose. The *excretion by the milk* is attested by the anitrachitic activity of butter, which is increased by feeding cows irradiated yeast. The diet of the mother during pregnancy and breast feeding therefore influences the susceptibility of the infant to rickets (Hess, 1923). *Storage* of viosterol has been demonstrated (for dogs) in the liver, adrenals, lungs, spleen and kidneys; none in the heart, brain, skin and pancreas (Coppens and Metz, 1933). Mammalian lung, however, and presumably other tissues contain enzymes that destroy the vitamin, so that it does not accumulate as in fish liver (C. D. Snyder, 1922).

Calcium-Phosphate Balance; Effects in Rickets.—Vitamin D appears necessary to maintain a normal balance between the calcium and phosphate of the plasma, and to the proper fixation of these for bone formation. It prevents and cures the defective bone development and all the other manifestations of human rickets and that produced in animals by diets deficient in viosterol. The improvement starts with progressive calcification at the epiphyses, and is evidently connected with the proper relation of calcium and phosphate in the blood. Vitamin D promotes economical utilization of calcium and phosphate and largely overcomes the disturbances of improper ratios of these elements in the diet. The significant feature of clinical rickets is a decrease of the inorganic phosphate of the blood plasma, often to half the normal level; the total calcium level is generally not diminished. The administration of viosterol appears to increase the proportion of inorganic phosphate of the plasma, gradually restoring it to normal in rickets, and to high values with excessive dosage. The phosphate excretion may be increased at the same time (Warkany, 1930). *The mechanism of the regulation* is obscure, but it is believed that the essential cause of rickets and of osteomalacia is inability to absorb sufficient calcium from the intestines (R. R. Hannon *et al.*, 1934). Tracer experiments with radioactive calcium in rats show that vitamin D increases the absorption of calcium, and secondarily of phosphate; and that it also acts directly on the mineralization of bone (D. M. Greenberg, 1945).

If the calcium and phosphate of the diet are abundant, the viosterol increase of inorganic phosphate in the plasma entails:

(1) A positive calcium balance; by a smaller excretion of calcium by the urine and feces, and a better absorption of calcium and of phosphate from the intestines. (2) Restoration of the calcium level of the blood if this has been deficient; and with overdosage, great increase of plasma calcium, similar to that produced by parathyroid hormone. The hypercalcemia is the most significant feature of overdosage. (3) Deposition of the normal bone salts in the epiphyses, and thereby correction of the rickets. Excessive dosage leads to hypercalcification of the epiphyses, of the large blood vessels and of other organs. (4) It is also claimed that viosterol returns an alkaline acid:base balance to normal (Liegeois and Lefevre, 1929), and that it shortens the coagulation time of the blood. (5) *If the calcium and phosphate of the diet are low,* viosterol increases these elements in the plasma, at the expense of the skeleton, and large doses produce osteoporosis.

Ca and P Level of the Plasma.—With normal diet, vitamin D increases the phosphate considerably more than the calcium level (L. J. Harris and Stewart, 1929). Lowering of the inorganic P level to half of the normal, 5 or 6 mg. per 100 cc., is an early and important sign of rickets in babies. Treatment with vitamin D restores this promptly to normal. The plasma calcium is not greatly lowered in uncomplicated rickets, but is low in infantile tetany, rachitic or other. It is also promptly restored by vitamin D.

Administration of Calcium and Phosphate.—Viosterol, as also parathyroid hormone, slows the rate at which *intravenously injected calcium chloride* leaves the blood stream (S. Freeman, 1936). *Feeding calcium gluconate,* to dogs, produces little increase of the blood calcium; but marked increase if viosterol had been administered. *Feeding with dicalcic phosphate,* however, caused but little rise in either the calcium or phosphate level of viosterol-treated dogs (Jones and Rapoport). The temporary rise of phosphate level on oral administration of *disodium phosphate* to rabbits or babies is greatly increased by vitamin D (Warkany). The *calcium content of bile* from hepatic duct fistula dogs, normally about 14 mg. per 100 cc., rises on viosterol administration only if the blood calcium rises. Raising the calcium of the plasma to 20 mg. raised that of the bile to 60 mg. per 100 cc. (K. K. Jones and Laing, 1934). *Retention of Ca and P* follows vitamin D administration, on any diet, in normal and rachitic children as well as animals. In clinical rickets the balance of calcium and phosphate is subnormal, with increased excretion of phosphate and calcium in the feces, and decreased calcium output in the urine. Vitamin D administration increases the retention of both Ca and PO_4 and strikingly reduces their excretion, and increases the urinary Ca output (Shohl, review, 1935). The *fate of phosphorus under vitamin D* has been traced in rachitic rats with the aid of radioactive P_{32}. Vitamin administration increased the absorption of the phosphate, administered by stomach tube, by only 10 to 15 per cent. It increased the P_{32} in the inorganic P of the bones by 40 per cent; and also markedly in the protein and ester P of bone, more than in muscle, and almost as much as in urine. That of the lipoid fraction of bone was not increased. The influence of vitamin D on the deposition of P in bone seems not due merely to increased absorption or supersaturation of inorganic phosphate, but involves a special effect on the organic phosphorus in the bone (W. E. Cohn and Greenberg, 1939).

The *bone changes in rickets* come from quantitative changes in the serum calcium or phosphate or both, below the critical precipitation level. They are primarily endochondral, beginning with failure of the normal progressive degeneration of the diaphyseal cartilage cells which precedes the entry of capillary loops, osteoblasts and calcium deposition. This results in continued growth and therefore increased thickness of the diaphyseal cartilage and of the osteoid bone matrix, lack of vascular growth into the cartilage and resorption of bone formed before the vitamin deficiency. In *osteomalacia* there is excessive resorption of bone, presumably to supply calcium for other vital processes. When vitamin D is given, the normal degenerative progression starts within twenty-four hours, with extensive vascular penetration (review, S. B. Wolbach and Bessey, 1942). The *enamel of the teeth* also is not properly formed during rickets, disposing toward subsequent caries. The British Commission of 1936 (ref., Biol. Abstr., *11:* 1989) concluded that the use of vitamin D in early childhood decreased the incidence of caries in children from 18 to 8 per cent.

The **effects of overdosage** depend chiefly on the hypercalcemia and are exaggerations of the therapeutic actions. The plasma calcium may rise to 22 mg. per 100 cc. after a single large dose; the phosphate level is also increased, the phosphatase is decreased markedly in the blood and kidneys, not in the liver and spleen, variable in bone (P. D. Crimm and Strayer, 1936; Freeman and Farmer, 1935). The Ca and P balance becomes negative and their excretion shifts from the feces toward the urine, with large loss of these elements from the tissues and bones. The ascent is gradual, and the maximum level is not attained for four or five days. A single dose, even if large, does not produce permanent ill effects, but continued administration results in the depressive symptoms of hypercalcemia, analogous to overdosage with parathyroid hormone. These develop in ten to thirty-six days, varying with the kind of animal. The first sign is loss of appetite; then lassitude and drowsiness, pallor, emaciation, often diarrhea, bloody discharge from the nose, flabbiness of muscle, renal irritation, albuminuria and nitrogen retention. Calcification of bone is hyperactive, and metastatic calcification occurs in various situations; clinical metastases are reviewed by J. M. Bauer and Freyberg, 1946. Necroses of the liver, kidneys and heart muscle occur even in the absence of calcification. If the overdosage is pushed energetically in animals, death results in one to four weeks (Blunt and Cowan, 1930; Shohl, Goldblatt and Brown, 1930; T. D. Spies and Glover, 1930; C. I. Reed, 1934; G. W. Covey and Whitlock, 1946.)

The toxic symptoms are not necessarily parallel to the calcium level. When they have developed, discontinuance of the viosterol does not generally result in recovery (Reed and Thacker, 1931), and the hypercalcemia outlasts the administration for several weeks. The susceptibility varies in different animals and individuals, but the margin of safety is wide. With the purer products, toxic effects require 1000 to 100,000 times the therapeutic dose (*cf.* Hauch, 1934; clinically, Shelling and Jackson, 1934; Spies and Hanzal, 1934). Reed and Struck, 1937, claim that men and dogs generally survive 20,000 units per Kg. per day indefinitely, without toxic effects, but this is not generally accepted as safe. Indeed, L. J. Harris concludes that the margin between the optimal and harmful dosage is much smaller in the human than in rats. Clinical intoxications attributed to massive doses are reported by P. A. Tumulty and Howard, 1942, and by Yeager, 1946. The toxicity is due partly to other more toxic sterols ("toxisterol"; Laquer and Linsert, 1933) whose ratio to viosterol varies with different methods of irradiation (Hoyle, 1930; Holtz and Schreiber, 1930). However, large doses of pure crystallized "calciferol" also produce analogous toxic effects (Dale, 1932; A. M. Hartman, 1937).

The *pathologic changes in overdosage* consist primarily in deposition of calcium phosphate, first in the epiphyses and lumen of the long bones, at the expense of the shaft. The resulting premature calcification arrests the growth of young rats (J. A. Collazo, Robino and Varela, 1929). Calcium deposits also form in the thoracic aorta and other large blood vessels (A. Schiff, 1930) and especially in the renal tubules, also in the heart, stomach and bronchi (Shohl and Brown, 1930; Hauch, 1934). The calcium mobilization finally occurs by depletion of the skeleton, with osteoporosis; the ash of the bone may be reduced by half. Congestive changes occur in the gastro-intestinal tract, and degenerative lesions in the heart muscle (review, S. B. Wolbach and Bessey, 1942). Dogs develop persistent rise of blood pressure (H. Handovsky, 1937). Lead, radium, thorium and polonium, if they have been deposited in the skeleton, are also mobilized by viosterol, but not so actively as by parathyroid hormone. The *teeth* (of rats) grow more slowly, the dentine is at least not increased, but the cementum is thickened and fused with the alveolar bone (J. Weimann). In dogs, the calcium content of the dentine is not changed by prolonged administration of heavy doses, sufficient to cause markedly increased x-ray opacity of the bones (E. W. Fish, 1935). The effects on dental and paradental structures are reviewed by H. Becks, 1942.

A single massive dose of D_2, 314,000 to 530,000 I.U. per Kg. administered to young dogs killed nearly half of the animals within two weeks, with the symptoms of anorexia, polyuria, bloody diarrhea, excessive thirst and prostration. The other dogs survived over eight months. Their serum calcium remained high for six months, with marked Ca and P retention. Autopsy showed excessive calcification of the lungs, moderate in the heart and kidneys, and striking abnormalities of the teeth and jaws (A. F. Morgan *et al.*, 1946).

Differences of susceptibility to overdosage are wide. That of *species* generally parallels their susceptibility to parathyroid hormone (N. B. Taylor, Weld and Sykes, 1934); but chickens are much more susceptible to viosterol poisoning than to the hormone. *Individual susceptibility* is markedly increased by age (Demole, 1929); by high Ca and low PO_4 diet; and by the weakness induced by rachitic diet. It is not affected by iodide administration (Hauch, 1934). It increases with the duration of the administration, and with more moderate overdosage it may not become manifest till the third or fourth generation (review, Clouse, 1933). *Exclusion of short wave lengths* in the irradiation is reported to diminish materially the production of toxic components (H. Schneider and Sperti, 1926; Reerinck and van Wijk, 1930).

Relation of Viosterol and Parathyroid.—The similarity of action suggested that the vitamin might act on the parathyroid gland; this is not so, for its effects occur after removal of the glands (Dale, 1932).

Comparison of Vitamin D and Parathyroid Hormone.—The effects of overdosage are similar, but the mechansim appears to be different. Both raise the calcium level of plasma, viosterol slowly and parathyroid dramatically; but parathyroid does this by lowering the PO_4 level, while vitamin D tends to raise the PO_4, especially in rickets, and may thereby even lower the Ca level and produce tetany (Collip, Pugsley *et al.*, 1934). The difference in susceptibility of animal species also indicates a different mechanism: the toxicity of viosterol, expressed as units per Kg., is a third less for rats than dogs; with parathyroid hormone, it is less than an eightieth (J. H. Jones, 1936).

Therapeutic Use.—Viosterol prevents rickets and cures all its effects and symptoms, including the tetany and spasmophilia; also when these occur as calcium phosphate unbalance without other symptoms of rickets (Hess, Lewis and Rivkin, 1929). It is effective in osteomalacia and in parathyroid deficiency. Viosterol may be given to nursing mothers to prevent a negative calcium balance. It has been advised to accelerate the healing of fractures (Roi, 1929), and to prevent and arrest dental caries (P. G. Anderson *et al.*, 1934); it would presumably be useful if there is a rachitic background, but otherwise the efficiency remains to be established. It has been claimed that viosterol secures calcification of the lesions of experimental tuberculosis (Levaditi and Po, 1930; Simonnet and Tanret, 1931; de Savitsch, 1934), but the practical significance of this is not certain. Beneficial results have been reported from massive doses in chronic arthritis, allergic disorders and psoriasis, but the evidence is not convincing.

In *rickets and its related conditions*, vitamin D is practically specific, for treatment as well as for prophylaxis. It may take the place of direct sunlight or ultraviolet irradiation of the skin in this regard, although exposure to sunshine also has other effects. Even nonrachitic children show seasonal variations in the plasma phosphate level, which rises in spring and summer. The *regulation of Ca and P metabolism* is probably useful for general health, in adults as well as infants, especially if the income of these elements is faulty; but data regarding this are inadequate. *Growth* of the body is conditioned on growth of the skeleton and may therefore be limited by inadequate income of vitamin D or calcium or phosphate. *Injurious effects of faulty Ca and P metabolism on tooth formation* in infancy, and such caries as may be dependent on them, would tend to be prevented by adequate vitamin income. In *parathyroid deficiency*, vitamin D is useful to keep up the calcium level until adjustment of the level has been reestablished (Brougher, 1928, 1932). Its effects are slower than those of hormone injections, which restore the calcium in four or five hours; viosterol requires thirty to thirty-six hours. On the other hand, the restored level endures longer after viosterol (four to five days) than with the hormone injection (thirty-six hours) (Jones, Rapoport and Hodes, 1930). It is more effective if it is administered before the operation (J. C. Brougher, 1928; Hess, Weinstock and Rivkin, 1929). **Dihydrotachysterol**, one of the activation products of ergosterol introduced by Holtz, Gissel and Rossmann, 1934, has been recommended as especially effective in maintaining the plasma Ca continuously at the normal level, without undesirable effects. A liberal calcium income should be provided (MacBryde, 1938; Albright, 1939; see under Parathyroid). Dihydrotachysterol is reported highly effective against diffuse scleroderma caused by disturbed calcium metabolism consequent on parathyroid injury in subtotal thyroidectomy (E. T. Bernstein and Goldberger, 1946).

Chronic Arthritis.—Apparently beneficial effects from massive doses were reported by I. Dreyer and Reed, 1935; but they are variable, about as with other lines of treatment (Vrtiak and Lang, 1936). P. S. Hench, 1946, concludes that it does not give even symptomatic relief in rheumatoid arthritis, and does not justify the risks of large dosage. *Allergic disorders,* hay fever and asthma have also been treated with massive doses, at least 200,000 units daily, with claims of relief, not correlated with changes in the plasma Ca or K level (Hathaway, Rappaport, Reed and Struck, 1936). The results are uncertain, and the harmlessness of such doses appears doubtful. *Psoriasis* appears sometimes improved by similar doses (300,000 to 400,000 units, Ceder and Zon, 1937), but the same limitations apply. A fourth of the patients showed evidence of incipient overdosage. *Keratoconus,* which may be produced in dogs by D deficiency with low Ca income, is reported to be improved clinically by vitamin D administration (A. A. Knapp, 1938). Beneficial results from vitamin D administration have also been reported in the *bleeding tendency of obstructive jaundice* (L. B. Johnson, 1937), and against the *toxemia of pregnancy* (G. W. Theobald, 1937; references in the review of Park, 1938).

The **daily requirement of vitamin D** is greatest at birth and decreases progressively during infancy. It is not accurately known and varies with conditions, but the following units may be considered adequate (up to double these quantities would proabably be better): prematurely born infants, 600 to 800; full term infants, children and adolescents, 300 to 400; adults, 135; in lactation and pregnancy, 800 units (Jean and Stearns, 1938).

Rickets does not develop in the majority of full term *infants* fed with milk containing 135 units per quart, but 400 units is needed for certain protection. If given as cod liver oil or as viosterol in oil, it is safer and better to use 800 to 1000 units per day. A few observations indicate that 1500 units may decrease appetite and so retard growth. Care must be used that the oil does not run down the trachea and produce lipid pneumonia. Breast fed infants require less than those fed on cows' milk, but it is better to give the same dosage. With *children* after the second year, the needs decrease with each year, but it is advisable to continue the administration throughout the period of growth, as 750 cc. of milk with 300 or 400 additional units. *Adults* appear more efficient in absorbing calcium than the average child, and do not need to add vitamin D to the ordinary diet—a total of 135 units is certainly adequate—except for those who are quite deprived of exposure to the sun, such as invalids and nightworkers. In *pregnancy,* however, normal calcification of the fetus is influenced by the vitamin intake of the mother and it is advisable to take at least 800, better up to 1000 units, as viosterol and 1.5 Gm. of calcium as $CaHPO_4$. During *lactation,* the drain on the mother is more severe than during pregnancy, and it seems necessary to take at least 1½ quarts of milk (equal to 1.8 Gm. of calcium) and 800 units or more of viosterol.

In *active rickets,* the prophylactic dosage causes marked improvement, but because the speed of the cure increases with the dosage (Bills), 1200 units should be administered daily; in refractory cases this may be increased to 20,000 units daily for infants, 50,000 for children (Parks, 1938). *Toxic effects from overdosage* need not be apprehended unless the daily dosage exceeds 20,000 units, and not then so long as the Ca and PO_4 level of the plasma remains normal. Plasma calcium above 12 mg. per 100 cc. indicates danger; also calcium casts in the urine. The symptoms are rather indefinite. Nausea is invariably present, sometimes nocturia (Park, 1938). Large doses should not be administered in renal insufficiency, nor to old people.

A single massive oral dose of 600,000 units is reported to prevent the development of rickets during fall and winter, as also monthly doses of 100,000 units from October to April. No untoward effects were noted (A. C. Rambar *et al.,* 1943).

Vitamin D milk has the advantage that it furnishes calcium and phosphate with the vitamin. Three forms are available: (1) "*Irradiated Milk,*" activated by direct exposure to ultraviolet light, contains the vitamin, probably activated 7-dehydrocholesterol. It is generally made to contain 135 units per quart, and cannot be increased much beyond this without acquiring a disagreeable taste. (2) "*Fortified Vitamin D Milk,*" adjusted to 400 units per quart by the addition of cod liver oil concentrate or viosterol. (3) "*Metabolized Vitamin D Milk*" or "*Yeast Milk,*" the milk of cows fed with irradiated yeast, and adjusted to contain not less than 400 units per quart, as viosterol. For equal unit dosage all three are equally effective in protecting infants against rickets, as judged by the roentgen picture and the serum Ca and PO_4 (Gerstenberger, Horesh *et al.,* 1935).

Parenteral administration of viosterol, by intravenous or peritoneal injection, is more effective in dogs than comparable doses by mouth (Reed and Thacker, 1931). This would be particularly desirable during acute infections, especially of the gastro-intestinal tract, when vitamin D may be poorly absorbed; but it has not been well worked out clinically. *Application of vitamin D to the skin* gives sufficient absorption to cure clinical and experimental rickets; fatal hypervitaminosis has been produced in animals by this route (review, J. J. Eller and Woelff, 1930).

PREPARATIONS.—See Index for Cod Liver Oil.

*Synthetic Oleovitamin D, U.S.P., a solution of activated ergosterol (Viosterol in Oil, N.N.R.; Liquor Ergosterolis Irradiati, B.P.) or of activated 7-dehydrocholesterol (D_3) in vegetable oil. The label must specify the sterol. Each Gm. contains not less than 10,000 U.S.P. units of vitamin D. The activity of vitamin D preparations is determined by comparing their antirachitic activity with that of the official Standard Preparation of antirachitic vitamin by curative and prophylactic tests on young rats on rachitogenic diets. (The unit corresponds to 0.025γ of crystallized calciferol.) It is a clear, light yellowish, oily liquid; odorless; bland taste; slightly sol. in alc.; miscible with ether and chloroform. Dose, 1000 units; 0.1 cc., 5 drops (prophylactic daily dose for an infant); 3000 to 4000 units, 0.3 to 0.4 cc., 15 to 20 drops (curative daily dose for an infant); larger doses may be given in severe cases.

Calciferol (Crystalline vitamin D_2; 9||10 ergostatetraene, *Drisdol*), prepared by activation of ergosterol by ultraviolet light or electronic bombardmnte. A microgram of the crystals corresponds to 40 U.S.P. units. It is marketed as *Drisdol in Propylene Glycol*, N.N.R., 1 cc. containing 0.25 mg., equivalent to 10,000 units, with a dropper adjusted to deliver 250 units per drop to correspond in potency with Synthetic Oleovitamin D. The propylene glycol renders it miscible with water. It is administered in milk, water or orange juice, *not* undiluted. The prophylactic and curative dose is stated as 2 drops in milk, 8 to 20 drops in watery liquid.

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STRONTIUM

This cathion resembles calcium, and may take its place in some of its characteristic pharmacologic relations; but it is much weaker and also less toxic; however, acute and chronic toxic effects have been described (M. Comel, 1930). Strontium has no therapeutic indication. The isotope is being tried to convey radioactivity to bone and marrow.

Like Ca, strontium hastens the coagulation of blood, although it is much weaker (Howell, 1914). This action is not shared by Ba or Mg. In dilute solutions only small amounts are absorbed from the stomach; none from the intestine, since it is converted into phosphates. It leaves the blood rapidly, so that no trace may be detectable there twenty-four hours after its administration. When about 250 mg. of Sr were injected by vein into normal persons for five days, 85 to 135 mg. were excreted for seven days; 93 per cent of the excretion was by the urine (McCance and Widdowson, 1939). The level of plasma calcium may be lowered or remain unchanged. The strontium is deposited in the bones, like calcium. This is mobilized if the parathyroid glands are excised (Andersch and Fay, 1939). Strontium salts, when administered orally to dogs, are excreted largely by the feces; when injected intravenously, by the urine (M. Fay *et al.*, 1942). It increases the elimination of uric acid. Cows excrete 8 to 11 per cent of intravenously injected strontium in the *milk* of 102 hours. Its administration to young animals or in intra-uterine life disturbs the bone formation. The osteogenetic tissue is stimulated, but the bones are imperfectly calcified, since the Ca is deficient and the Sr is deposited imperfectly (Lehnerdt, 1909, 1913; Kinney and McCollum, 1923).

Effects of Strontium.—Injection of small doses of $SrCl_2$ raises the blood pressure chiefly by stimulation of the cardiac muscle. The respiration is also stimulated. Large doses produce apnea, inhibit the heart and cause death by cardiac arrest with cats; by respiratory failure with rats. The intravenous toxicity for rats is slightly higher than that of calcium; for mice it is considerably less (V. V. Cole *et al.*, 1941). Isolated vessels are constricted (Boriani, 1939). The effects of strontium on the *autonomic system* differ from those of calcium. However, strontium chloride can take the place of calcium chloride in Ringer's solution for excised frog heart and rabbit intestine, but fatigue sets in more quickly (Ono, 1927). The bronchioles are constricted, as with barium (Boriani, 1939).

Anion of Strontium Salts.—Strontium salts have been used, in same dosage as the sodium salts, mainly on the supposition that the anions would be more slowly absorbed, and would therefore have a more gradual and milder action. This theory is without foundation. Iodide, for instance, is absorbed with the same rapidity as from the potassium salt (Krahulik and Pilcher, 1918); and the "toxic" effects of strontium salicylate are just as pronounced as with the sodium salt (Blankenhorn, 1916).

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OXALIC ACID AND OXALATES

Oxalic acid and the oxalates exert a strong acid action, resulting in local irritation and corrosion. In addition, they produce violent stimulation, and later paralysis. These actions are completely antagonized by the addition of Ca. The oxalates have some toxicologic importance, but no therapeutic interest. The small quantities which occur in many vegetables (rhubarb, and so forth) are ineffective if these are consumed in the ordinary amount (review, H. Jeghers and Murphy, 1945).

Oxalate Poisoning.—When taken by mouth, the oxalates are *readily absorbed*, and poisoning is not infrequent from confusion with other salts. The *symptoms* are, at first, those of a local caustic, especially when the acid was used; then those of rapid collapse, possibly preceded by convulsions. The pulse is small and weak. *Death* by oxalic acid and oxalates usually occurs much more quickly than by other caustic substances. This is of diagnostic importance. (In one case death took place in ten minutes.) Sometimes fatal collapse may occur after hours of relatively slight symptoms (O. H. Brown and Scott, 1912; review, J. Pohl, Heffter's Handb, *1*:860).

A study of seventeen human cases of oxalic acid poisoning is reported by Wichern, 1912. The *fatal dose* varies with the concentration. The smallest recorded amount is 5 Gm. *Metabolism* is markedly depressed in oxalate poisoning, especially the production of carbonic acid. The respiratory quotient falls (Corley, 1902). The urines in Wichern's cases were scanty, with traces of albumin, and rarely calcium oxalate crystals. Polyuria developed later. Hemorrhagic nephritis was not observed. The kidneys of a fatal clinical case showed marked *renal injury*, cloudy swelling, hyaline degeneration and sclerosis of the tubules (Többen, 1938). The *toxic phenomena of oral poisoning of dogs* were studied by E. Rost. *Cumulative action* is observed after continued feeding of rabbits with oxalates or citrates (Salant and Swanson, 1918). Többen, 1938, found renal injury similar to the clinical poisoning.

Rhubarb Leaf Poisoning.—Serious and even fatal poisoning has been attributed to the eating of boiled rhubarb leaf "greens." The leaves contain about 10 grains of oxalate per pound, and this has been held responsible for the poisoning (J.A.M.A., 1917, *68:* 1928; 1919, *73:* 926). The connection appears rather doubtful. Data on the *oxalate content of vegetables* are given by Arbenz, 1917, and by E. H. Kohman, 1934. Traces of oxalate occur in practically all vegetables and fruits. Spinach and similar greens contain 0.3 to 0.7 per cent of oxalate, equivalent to about 10 per cent of the dried weight. Calcium oxalate is not absorbable, and the oxalate in vegetables interferes with the utilization of their calcium (S. K. Talapatra *et al.*, 1942). Addition of 8 per cent of spinach to the diet of rats may result in serious calcium deficiency (Kohman, 1939).

Treatment of Oxalate Poisoning.—The chemic *antidote* is calcium in any form, calcium chloride and lactate, chalk, lime water, and the like (Husemann). Liberal quantities of water should be given to prevent the deposition of crystals in the kidneys. Calcium lactate should be administered by vein; magnesium sulfate should be given as cathartic.

Fatal sodium oxalate poisoning in mice may be completely antagonized by *parathyroid hormone* (Kochmann, 1938). Experimentally, magnesium injection has proved of some value by quieting the stimulation (Gates and Meltzer, 1917; Gates, 1918).

Fate.—Oxalates are resistant to oxidation in the animal body, but it seems certain that a limited amount is oxidized. The *excretion* (92 to 95 per cent after hypodermic injections) occurs almost completely by the kidneys. In *rabbits* with a uniform diet, the urinary excretion is fairly constant, the fecal excretion varies widely. With intravenous injection it is excreted rapidly by the urine, but not quantitatively. The oxidation is reported to be increased by insulin (Lucia, 1929). Its absorption from the intestines depends on the Ca content of the food and the pH of the intestines (Oikawa, 1938). With oral administration to *dogs*, 72 per cent was recovered unchanged in nine days, 63 per cent in the urine. The remainder was probably destroyed by the intestinal bacteria. On a normal diet, dogs excreted 213 to 330 mg. per day, of which 94 per cent was in the urine and 6 per cent in the feces (Orzechowski *et al.*, 1935). The fresh urine contains mainly oxaluric acid, but on standing this decomposes into urea and oxalic acid, which forms calcium oxalate. This is almost insoluble and occurs as envelope-shaped crystals, which are diagnostic of oxalate poisoning. The crystals may be excreted in such amounts as to block the urinary tubules, and may thereby possibly lead to *nephritis*, or retention of urine and uremia. Calcium oxalate, in rod-shaped crystals, may be found in all the organs, but it may be absent from these in acute poisoning (Mürset, 1885). In administering sodium oxalate to dogs orally and parenterally, acutely and slowly, the highest content was found in the kidneys, and lasted long after the administration. There may be severe tubular necrosis and intraepithelial crystal deposits (Heubner and Hückel, 1935).

The blood normally contains traces of oxalate, not more than 0.48 mg. per 100 cc. Older figures of 2 to 4 mg. were based on faulty method (J. F. B. Barrett, 1943). Oxalic acid is formed, in dogs and rabbits, by the oxidation of glyoxal and glycolic acid (Herkel and Koch), of ethylene glycol and its monoacetate, but not by a variety of other ethylene derivatives (F. H. Wiley *et al.*, 1937).

The *calcium balance* is rendered negative by soluble oxalates, through the precipitation of calcium in the digestive tract (Kohman and Sanborn, 1935).

Tooth enamel solubility is decreased *in vitro* by sodium oxalate, as with fluoride, and is more effective than the latter to counteract erosion by dilute acid in living rats. Spinach does not have this effect, as its oxalate is not sufficiently soluble (Gortner, Restarski *et al.*, 1946; Gortner, McCay *et al.*, 1946).

Blood coagulation is prevented *in vitro* by the addition of 0.1 per cent of ammonium, potassium or sodium oxalate. This is due to calcium precipitation, and addition of calcium chloride restores the coagulability (Arthus and Pagès). However, intravenous injection of 20 mg. of oxalic acid is reported as *hemostatic*, shortening the coagulation time (without appreciable effect on prothrombin time), and producing immediate decrease or cessation of bleeding from major operative procedures or carcinoma, without bad effects (A. W. Blain and Campbell, 1942).

Intravenous Injections in Mammals.—The oxalates first affect the *central nervous system* in its whole extent, from mental functions to reflexes, producing stimulation with convulsions, and then *paralysis*, the latter being more conspicuous with large doses. The medullary centers are especially involved. The *asphyxia* causes glycosuria, and possibly indicanuria. The temperature rises. *Death* occurs from respiratory paralysis, except when the poison is injected directly into the circulation, in which event it may paralyze the cardiac muscle (slowed heart and fall of blood pressure, v. Vietinghoff-Scheel, 1901; Starkenstein, 1914). *Repeated injections* of sodium oxalate into rabbits result in *hypertension*, lasting about twelve days, with gradual return to the normal level, but with marked instability. It is probably caused by the nephritic injury (Arnott and Kellar, 1935). Oxalates, injected with Mg, increase the anesthetic effect, presumably by inactivating the antagonistic Ca (Gates and Meltzer, 1914),

Calcium and Phosphate Balance.—Intravenous injection of sodium oxalate or citrate into dogs immediately lowers the plasma Ca, more so with oxalate than with citrate. Recovery of the Ca level occurs rapidly, and is completed in a few hours. The phosphate level is slightly depressed during the Ca fall, rises markedly with the Ca recovery, and may continue elevated for twenty-four hours. The recovery is attributed chiefly to mobilization of calcium phosphate from the bones through intermediation of the parathyroid (Tsai and Hsu, 1930).

Actions on Peripheral Autonomic Nervous System.—The oxalates act like deprivation of Ca; *i. e.*, they increase the sensitiveness to epinephrine and pilocarpine; but they diminish the excitability to electric vagus stimulation (Chiari and Froelich, 1911). In *excised intestines*, the calcium precipitants increase the tone and the pendulum movements (Starkenstein). The *response of the heart to vagus stimulation* is abolished by intravenous injection of sodium oxalate (or citrate) in turtles (G. D. Shafer). Injections of oxalates produce slowing and weakening of the *frog heart;* with stronger concentrations prompt diastolic arrest, first of the ventricle, then of the auricles. This can be removed completely by rinsing with Ca solution (Januschke, 1909). Washing with NaCl alone gives much poorer recovery (Gros, 1913). Similar effects are seen with perfused mammalian hearts (Salant and Hecht, 1915).

Skeletal Muscle.—Dilute solutions of oxalates (or other precipitants or inactivators of calcium) applied directly to skeletal muscle cause fibrillation, tetanus and contracture. Diminution of the proportion of Ca by any other means has the same effect. Larger doses of oxalates depress the excitability and force of the skeletal and cardiac muscles.

Glycogenolysis of slices of rat liver is damaged by oxalates, and is arrested by quantities which would bind only a tenth of the calcium. Decrease of calcium by 30 per cent does not check the glycogenolysis in the absence of oxalate. This oxalate action is therefore not explainable by calcium precipitation, but must be more direct. However, addition of calcium antagonizes oxalate by precipitation (Brock *et al.*, 1940).

Intact frogs show progressive and descending loss of reflexes, fibrillary twitchings, central paralysis, finally cardiac arrest. This is also promptly removed by Ca and Sr.

Lower Organisms.—Oxalates are toxic to all life except to a few lower fungi which do not contain calcium. They are toxic to most plants, but certain species contain soluble oxalates. In algae the main histologic changes are seen in the portions richest in calcium—nucleus and chlorophyl (O. Loew, 1912). Oxalic acid is probably a constant product of metabolism, and one of the functions of calcium is to render it harmless.

FLUORIDES

Sodium fluoride, NaF, is a general protoplasmic poison, of some toxicologic importance and considerable scientific interest. Its use to poison cockroaches and rats, as also that of sodium fluosilicate, has led to human fatalities. It produces local necrosis of mucous membranes. After absorption it causes acute and chronic poisoning, especially gastroenteritis, even with parenteral administration, collapse, and hepatic and other visceral degeneration, with nutritional disturbances. The long-continued ingestion of small quantities, such as occur in the water supply of some districts, injures enamel formation, causing "mottled enamel" and other abnormal bone formation. It also has a protective action against dental caries. The acute effects may be due partly to disionization of calcium, similar to oxalates; but other factors are more important, especially the destruction of various enzymes. Sodium fluoride is readily soluble in water (1:25); but the sparingly soluble calcium salt is almost equally liable to produce chronic poisoning. Inorganic fluorine compounds, such as the fluosilicates, are generally toxic by liberating fluoride ions. The gaseous aliphatic fluorine compounds have a low toxicity and are discussed with the aliphatic narcotics. (Reviews, De Eds; McClure; Roholm, 1937, 1938; D. A. Greenwood, 1940.)

Occurrence in Nature.—Fluorine is one of the most widely distributed elements, ranking about twentieth in the first mile of the earth's crust. It is found chiefly as *fluorspar*, CaF_2; aluminum fluosilicate; *cryolite*, a double fluoride of aluminum and sodium, which is used extensively as a source of aluminum; *apatite*, a native calcium fluophosphate, $Ca_5(Cl,F,OH)(PO_4)_3$; and other minerals. The fluoride content of soils has been reported up to 0.15 per cent, averaging about 0.03 per cent. It has been demonstrated in the municipal water supplies of all large American cities (Churchill), often in quantities sufficient to produce mottled enamel.

Occurrence in the Body.—The wide distribution of fluorine compounds accounts for its normal presence in plants and animal tissues, generally as the sparingly soluble CaF_2. It probably does not serve a useful function (Jodlbauer, 1901). It was discovered in normal tooth enamel by Gay-Lussac and Berthollet in 1805. Gabriel, 1893, confirmed its normal presence in bones and teeth. Smaller quantities are found in the epidermis, hair, thymus, testes, blood, milk, and so forth (Gautier and Clausmann, 1913, 1916). Zdarek, 1910, found it present in the entire human body, but relatively richest in the liver, kidneys and bones. The *fluoride content of soft tissues* is as follows, mg. per 100 Gm. of dried tissue: epidermis and hair, 6 to 17; glands and blood, 1 to 4; cartilage and muscle, 0.04 to 0.5. W. C. Dreesen and Sievers, 1946, state the mean content of the blood in normal men as 0.01 mg. per 100 cc.; of urine as 0.2 to 0.4 mg. per liter; the upper safe limit of urinary excretion as 4 to 5 mg. per day.

The quantitative methods are not entirely satisfactory; but Gautier and Clausmann, 1916, made extensive studies on the occurrence of F in *foods*, and found the average 0.6 mg. per 100 Gm. of fresh material. The modern data, reviewed by Roholm, show wide variations. Sea food is relatively rich; but the largest amount, aside from vegetables sprayed with fluoride, is found in bone and teeth. *Bone ash* contains normally from 17.5 to 123 mg. per 100 Gm. (Gautier and Clausmann). Other data run from 10 to 30 mg. per 100 Gm. of fresh bone. It is probably present as an apatite, $3[Ca_3(PO_4)_2]CaF_2$. Teeth and enamel contain about the same amount. The content rises with the age of the individual. Fossil bones contain more than recent bones, presumably because their calcium precipitates the fluoride of the ground water. Addition of sodium fluoride to the food and drink of adult dogs for over two to eighteen months raised the fluoride content of the *dentine* progressively from 18 to 72 mg. per 100 Gm.; that of the *enamel* showed little if any increase (E. W. Bodine, 1942).

Use as Insecticide.—Fluoride appears to be more toxic to insects than to higher animals, perhaps because their Ca and P content is lower (Marcovitch). However, the action is not understood. *Spraying* of vegetables and fruits with cryolite is effective, but the U.S. Government regulations (1938) provide that the food as marketed must not contain more than 0.02 grains of fluoride per pound (2.8 parts per million). If *cryolite* is added to the food, its slow solubility makes it about half as toxic, and gives about half the retention, as the same amount of F in the form of NaF. When dissolved in drinking water, however, the effects are identical (Marcovitch and Stanley, 1938; R. J. Evans and Phillips, 1939; M. Lawrenz *et al.*, 1939). The retention in bones of growing rats is somewhat less if cryolite is fed intermittently than if the same total is taken continuously (Lawrenz, Mitchell and Ruth, 1940). Sodium fluoride is used extensively against *roaches.* It may be mixed with an equal quantity of flour and wrapped loosely in paper, so that it can be reached and eaten by the insects. The success with this method is limited, but it is practically devoid of danger, unless the powder itself is eaten; it should be kept out of the reach of children, and adults should be cautioned against it. Promiscuous dusting with the powder is more effective and also more dangerous.

Antiseptic Action.—Sodium fluoride is antiseptic in concentrations of about 0.25 per 10,000, and germicidal in 1:200. Before its toxicity was generally recognized, it was used for irrigations and moist dressings (0.25 to 10:10,000), and even for the preservation of food (10 to 15 mg. per liter). These uses are too dangerous. J. Head, 1913, employed "*ammonium bifluoride*" in the treatment of pyorrhea (injection of 23 per cent solution around the loose teeth twice a week).

Local Action.—A 2 per cent solution of *sodium fluoride* kills the cells of mucous membranes, and produces corrosion. Oral administration of soluble fluorides and silicofluorides causes hemorrhagic gastro-enteritis.

Hydrofluoric acid produces vesication and deep and progressive destruction of tissue, suppuration, and painful slowly healing ulcers (Gay-Lussac and Thénard, 1809). This is not due merely to the acidity, for undissociated HF appears to penetrate through intact epidermis (Görlitzer, 1932). Slight exposure causes rubefaction and a burning sensation; 2 to 5 per cent solutions have little or no effect on human skin; stronger solutions produce a yellow, leathery change of the epidermis, and the corrosive effects as described. Local injection of calcium gluconate appears to arrest the process and to secure prompt healing (Paley and Seifter, 1940).

Acute Fluoride Poisoning.—Fatal acute and chronic poisoning in man has resulted from careless use of fluorides as vermin poisons, especially where it may be mistaken for baking soda or baking powder. The *phenomena of sublethal acute poisoning* are chiefly gastro-enteritis and collapse, and may run a rapid course, with sudden nausea and vomiting, abdominal burning and cramps, diarrhea, for three to six hours; stupor and weakness for thirty-six hours (Vallee, 1920, 0.23 to 0.45 Gm.; Sharkey and Simpson, 1933, literat.). *Fatal cases* develop muscular weakness and tremors progressing to clonic convulsions originating in the cord and higher centers (decalcification?), fall of blood pressure, general collapse, sometimes with grayish-blue cyanosis, dyspnea, arrest of the respiration and of the heart. Death occurs in a few minutes to ten hours or longer. Rigor sets in promptly. *Frogs* also show fibrillary contractions of the skeletal muscles which are arrested by section of the nerve (Tappeiner, 1889; human cases, Raestrup, 1925; Pietrusky, 1930; Zeyneck and Stary, 1931). The *gastro-enteritis* is not merely local, but occurs also if the drug is introduced by other channels, the intestinal epithelium being destroyed, while the cilia of the respiratory epithelium may still be moving (Siegfried, 1901). The primary injury is probably to the capillaries, the permeability of which is increased even by small doses (Asher, 1910). *Necropsies* show inflammation of the mucosae of the esophagus, stomach and small intestines, with petechiae, but without corrosions. It may be due to injury to the capillaries. The stomach generally contains 70 to 200 cc. of bloody fluid (Raestrup). Frequently there is also marked cerebral hyperemia and edema, and edema of the lungs with petechiae of the pleura and pericardium. Muehlberger, 1930, considered that the chief changes consist in congestion and hydropic degeneration of the liver and kidneys. Albuminuria is generally present. The *parathyroid glands* are reported to show marked degenerative changes in rabbits killed acutely by fluoride; and less severe effects in chronic poisoning (Pavlovic and Tihomirov, 1932).

Toxic Dosage.—Dangerous symptoms have been reported in man from 0.25 Gm. of sodium fluoride. Recovery has followed 0.5 Gm., and death has been caused by 4 Gm. The acutely fatal dose for mammals averages about 0.5 Gm. per Kg., by mouth; about 0.15 Gm. per Kg., hypodermically or by vein (Tappeiner, 1889).

Treatment.—Gastric lavage with calcium chloride followed by adsorbents (charcoal) should be tried; intravenous injection of calcium chloride might be useful. Fatal fluoride poisoning in mice can be successfully *antagonized* by parathyroid hormone, so that this may be used for the bio-assay of the hormone (Kochmann, 1938).

Fluoride on Calcium Metabolism.—Fluoride poisoning tends to lower the calcium level of the plasma. In rabbits on calcium deficient diet this may amount to 50 per cent in acute poisoning, 13 per cent in chronic poisoning (Jodlbauer, 1932). The plasma phosphate is also lowered in acute, but not in chronic, poisoning (Pavlovic and Bogdanovic, 1932). The calcium level may be but little lowered even in acute poisoning, and may be normal in chronic poisoning (J. A. Schulz, 1931; Greenwood, Hewitt and Nelson, 1935). The changes in the blood calcium level are not sufficient to explain the fluoride toxicity, even in acute poisoning. The antagonistic effects of calcium injection (Schlick, 1895) are due to defluorization, rather than to correction of a calcium deficiency.

Enzyme Processes.—Fluorides are strongly inhibitory to some enzymes, while others are little affected. Anaerobic *glycolysis* in yeast, muscles and other tissues is especially susceptible, the action resembling that from monoiodoacetic acid (F. Lipmann, 1930). Injection of sodium fluoride into the carotid artery depresses the *electric activity of the cerebral cortex* by momentary inhibition of cortical glycolysis (Moruzzi, 1938). *Other enzymes* that are strongly restrained include lipase, esterases and urease. Proteolytic and diastatic enzymes are not very susceptible. Salivary amylase is not affected even by fairly high concentrations (F. J. McClure, 1939). Alcoholic fermentation is inhibited, as is also the coagulation of blood or of milk.

Blood Coagulation.—The addition of 0.4 per cent of sodium fluoride renders shed blood noncoagulable. This is due chiefly to inhibition of the formation of fibrin ferment (Calugareatu), and not to precipitation of calcium, for the coagulability is not restored if the calcium is restored, but only if thrombin is also added. It has been suggested that the fluoride prevents the breaking up of the platelets and leukocytes, but this requires confirmation. The action may be due to the liver injury. Feeding sodium fluoride does not diminish the coagulability of the blood (Greenwood *et al.*, 1935). The *clotting of milk* by pepsin or rennin is inhibited by fluoride (Clifford), but occurs if calcium is added, so that the interference in this case is not with the enzyme action. *Lipase* is inhibited by NaF, 1:5000, and checked by 1:15,000,000 (Kastle and Loevenhart, 1900). Esterases which are inhibited include *phosphatase* (Lipmann, 1928; Kay, 1928); and *cholinesterase* (1:15,000), thereby increasing susceptibility to acetylcholine (Matthes, 1930; Kahlson and Uvnas, 1935). Fluoride interferes with the catalase and oxidase of *insect tissue extracts*, but not with the reductase (G. D. Shafer, 1915)

Glycolysis and Muscle Enzymes.—Sodium fluoride depresses the respiration of finely divided muscle, and still more the formation of lactic acid and the hydrolysis of glycerophosphoric and hexose-phosphoric acids. It acts differently from cyanide in this respect (F. Lipmann, 1928). The effect is due to inhibition of the magnesium enolase that converts 2-phosphoglyceric acid into 2-phosphopyruvic acid. (This conversion is also effected by zinc and manganese enolase, which are inhibited by cyanide; O. Warburg and Christian, 1941.) This inhibits the formation of lactic acid (Meyerhof, 1935). The muscle can perform work without raising its lactic acid content, by the more rapid decomposition of phosphagen, esterification of hexose with phosphoric acid, and splitting of adenyl pyrophosphate (Lipmann, 1930). It does not prevent the decrease of glycogen in muscle pulp, but inhibits and may reverse the glycogen breakdown in intact muscle (Embden). Muscle immersed in fluoride shows spontaneous fibrillary contractions, tetanus and rigid *contracture.* It is toxic to *nerve.*

Heart.—The SA and AV conduction is changed in the excised *frog heart* by 10 to 20 of NaF or 10 of CaF_2. The latter shows that the effect is not due to decalcification. The effects resemble those of monoiodoacetic acid, and may be ascribed to the changes in the intermediate carbohydrate metabolism of the cardiac muscle (Chang, 1938). With *dogs,* 20 to 70 mg. of NaF per Kg. lowers the blood pressure. The heart dilates temporarily, often with auricular flutter; then returns to normal; and finally dilates again, with sinus block, extrasystoles and ventricular flutter (Gottdenker and Rothberger, 1935).

The **excretion** of fluoride occurs chiefly by the urine (O. Schultz, 1889), considerably by the sweat (F. J. McClure, Mitchell *et al.*, 1945), and some by the feces. Some is also secreted into the milk, enough to cause the death of nursling rats (Goldenberg, 1928). It passes freely across the placenta to the fetus (M. M. Murray, 1936). Considerable may be *retained,* increasing the F content of the tissues (Tappeiner). Retention occurs in man with daily ingestion of 5 mg. (F. J. McClure *et al.*, 1945). In five instances of fatal clinical poisoning, the F content of internal organs ranged between 0.14 to 1.6 mg. per 100 Gm. (Gettler and Ellerbrook, 1939; improved test). The *normal daily exchange* for man was estimated by Gautier and Clausmann as: income, somewhat about 1 mg.; excretion by urine, 0.23 mg.; by feces, 0.80 mg. The food, exclusive of drinking water, averages 0.92 mg. per Kg. Variations of income and excretion are chiefly due to the domestic water supply. When this is practically fluoride free, the urine contains 0.3 to 0.5 mg. of F per liter. When the water contains 0.5 to 5 mg. per liter, the urinary concentration rises proportionately (F. J. McClure and Kinser, 1944).

Chronic Fluoride Poisoning.—Small quantities of fluride that produce no apparent effects when administered singly, lead to marked changes when their administration is continued. The smallest effective quantities, as drinking water or food, show only faulty tooth formation in children, "mottled enamel." *Mottled nails* are also an early sign of chronic fluorosis (L. Spira, 1943). Somewhat larger amounts, experimentally or in industrial exposure, may cause bone changes in adults, osteosclerosis in man, osteoporosis and osteomalacia in animals. Still larger amounts produce anorexia, anemia (probably by interference of the bone changes with the marrow) and cachexia, loss of weight and impairment of growth and impaired reproduction. The toxic effects are inverse to the *intake of calcium* (S. Ranganathan, 1941). They appear to be aggravated by dietary deficiency of ascorbic acid (J. F. Linsman and McMurray, 1943); this is practically important in India (C. G. Pandit *et al.*, 1940).

Endemic fluorosis, characterized by "*mottled enamel,*" exists in various areas of the world; in the United States especially in regions of the Rocky Mountains and Mississippi Valley, but to some degree in practically every state. It is a serious problem in Argentina. It was first described in 1916 by Black and McKay. Subsequent studies by McKay, 1926 and 1930, indicated its relation to the domestic water supply, and Churchill, 1931, showed spectroscopically that these waters contain fluorine. M. C. Smith, Lantz and Smith, 1931, found mottling in practically every person who had lived in one of these foci (St. David, Arizona) before permanent teeth erupted; and none in those who came there after this time. *Water supplies responsible for mottling* contain 2 to 7.2 mg. of fluorine per liter; none is reported with less than 0.3 mg. per liter, and practically none with 0.6 mg. per liter; slight with 1.7 mg. (H. T. Dean and Elvove. 1935). Not all the children are affected, the incidence increasing with the fluoride concentration. Change to water supply of lower content prevents further cases (Dean, McKay and Elvove, 1938). Significant delay of tooth eruption occurs with 2.6 mg. per liter, but not below (E. M. Short, 1944). *The fluoride may be removed from the water* by treatment with tricalcium phosphate, or magnesium oxide or hydroxide. Commercial calcined magnesite (MgO) is effective and cheap (Elvove, 1937). Ingestion of aluminum sulfate was also reported to decrease the dental injury (C. A. Kempf *et al.*, 1937); but R. J. Evans and Phillips, 1939, failed to obtain any protection by adding this to the fluorided food of rats; nor by administering vitamin A.

On the other hand, it has been demonstrated that children living continuously for the first twelve years of life in fluoride areas have a lower attack rate of *dental caries* than those in nonfluoride areas. It has not yet been demonstrated that the addition of fluoride to the water supply has this effect. The mechanism is not known. It has been suggested that it modifies tooth structure so as to decrease the solubility of the enamel in acid. Others believe that it checks the growth of

Lactobacilli; but there is no evidence that it is effective after the teeth are fully formed (report, J. Am. Dent. Assoc., *34*:345, 1947).

H. T. Dean *et al.*, 1941, observed that the prevalence of tooth decay tends to be inverse to the fluoride content of the water supply of the locality. This has been abundantly confirmed (F. S. McKay, 1945; Klein, 1945). A concentration of 1 ppm during the first eight years of life suffices, with little or no mottling. F. J. McClure, 1943, recommends that fluoride should be added to the water supply to bring it to this level. However, if caries does start in mottled teeth, it spreads rapidly (M. C. Smith and Smith, 1940). J. D. Boyd and Cheyne, 1946, point out that some tooth decay is almost universal, even in areas of endemic fluorosis, and it is often high in mottled teeth. After the teeth are calcified, topical application is probably more effective. J. W. Knutson and Armstrong, 1945, applied a 2 per cent solution of sodium fluoride twice weekly for eight to fifteen treatments. They report the caries incidence reduced by over half, both in the first and in the second year after treatment. However, the incidence of caries is not reduced in two years, as compared with a control group, by dentifrices containing 0.01 and 0.1 per cent of NaF (B. G. Biddy, 1945). Prophylactic cleansing with pumice powder containing 1 per cent of fluoride is reported to decrease the incidence of new caries by 25 to 43 per cent. A mouthwash containing 0.1 per cent, used three times weekly for a year, did not decrease the incidence (B. G. Biddy *et al.*, 1946). Other enzyme inhibitors, monoiodoacetate and menadione, also tend to reduce caries (M. Massler, 1944). Experiments on rats show that the fluoride is absorbed into the enamel (M. W. Perry and Armstrong, 1941). It should not be applied to cavities, for this leads to inflammation, abscess and necrosis of the tooth pulp (W. Lefkowitz and Bodecker). Topical application of fluoride also reduces the caries incidence in *rats* on caries-producing diet (Sognnaes, 1941). Oral administration restricts caries according to most observers (F. V. McClendon and Foster, 1941), and decreases the enamel destruction when an acid phosphate sucrose solution is ingested (C. M. McCay *et al.*, 1945, 1946).

Fluorine in food is at present of minor importance, unless the water content is also fairly high. However, the residue of fluoride spraying should be controlled by washing or peeling. It is also conceivable that extensive use of such insecticides may eventually enrich the fluoride content of the soil so as to raise the fluoride content of the crops In the meantime, however, insecticides of some sort are practically indispensable to the economical supply of vegetable food. *Bone ash* contains about 0.1 per cent of F, sufficient to produce tooth degeneration when fed to rats. Roholm, 1939, therefore advises against the use of bone ash as a mineral diet supplement for children or pregnant or lactating women.

The *changes in human teeth* consist of chalky white patches, often pitted and eroded. The mottling involves generally less than a third of the thickness of the enamel; if it disfigures seriously it can be removed by grinding or by 18 per cent hydrochloric acid (C. A. McMurray, 1941). Identical changes had been observed by McCollum and associates, 1925, in the *teeth of young rats* receiving small quantities of fluoride. The lower incisors are shortened by spontaneous fractures, leading to nonocclusion, and the upper incisors therefore continue to grow and curl backward. Chaneles, 1929, noted the dull, chalky color and roughening, and studied the histological changes. These were investigated in the teeth and jawbones by Pachaly, 1932, and W. Dittrick, 1932. They consist in deposition of hypoblastic, faultily calcified enamel and bone tissue. The enamel-forming cells are selectively vulnerable to fluoride, being injured by doses for which no other deleterious action has been demonstrated. Morphologic changes in the ameloblasts and their calcium globules may be seen an hour after injection of sodium fluoride (Schour and Smith, 1935). Dean, Sebrell and Breaux, 1934, describe the progression of the changes with increasing concentrations of NaF in the drinking water, from minute transverse brown striations with 25 parts per million; passing to irregular brown patches with 150 ppm; and becoming chalky and brittle at 300 ppm. These effects are not prevented by the administration of calcium, phosphorus, Na_2HPO_4 or parathyroid hormone (Sutro, 1935). *Dogs* develop mottled enamel, as in the human (Greenwood, Hewitt and Nelson, 1935); *cattle* and *pigs* show marked changes in the *mandibles*, with increase of thickness, roughing of the surface and enlargement of the medullary spaces (G. E. T. Taylor, 1929; Bethke *et al.*, 1933).

The *fluoride content of human teeth* is normally about 0.02 per cent of the ash; in rats on ordinary diet it is generally between 0.02 and 0.03 per cent (Bowes and Murray, 1935). Data for many other animals are reported by Klement, 1935. In industrial exposure of men to fluoride dust, with a probable daily income of 15 to 25 mg. of F for years, the tooth ash contained 0.25 per cent, about ten times the normal quantity (Roholm, 1938). On feeding small quantities of fluoride (8 to 14 parts per million of food) to rats, the F content of the dry bones increases to 0.02 to 0.065 mg. per 100 Gm., roughly proportional to the amount fed (G. Ellis and Maynard, 1936).

Bone changes are seen especially with industrial exposure to the dust of cryolite or phosphate rock, with larger fluoride income than would occur from water. With probable income of 15 to 25 mg. per day, the earliest roentgen changes are seen in about two and one-half years and become severe in about eleven years (Roholm, 1938). P. F. Moeller and Gudjonsson, 1932, found half of the workers exposed to cryolite dust affected. The changes consist in generalized osteosclerosis, involving all the bones, but especially spongy bone, including the spinal column. The density of the bone is increased, with preservation of the normal bone architecture, but change of the normal structure. The organic matrix is irregular, the calcium deposition is increased but irregular, calcareous deposits extend to the ligaments and muscles, and osteophytes form between the vertebral bodies (P. A. Bishop, 1936). Water supplies relatively rich in fluoride do not result in demonstrable skeletal sclerosis (P. C. Hodges *et al.*, 1941), nor do they influence the average height and weight, nor is the frequency of bone fractures increased (F. J. McClure, 1944).

Exposure to cryolite dust also develops other symptoms. Anorexia, nausea and vomiting appear early, but tolerance to these is soon established. Continued exposure leads to functional dyspepsia, rheumatic pain, obstipation and the osteosclerosis, demonstrable by roentgen examination. Postmortem examination of two workers exposed for many years revealed no visceral changes definitely attributable to the intoxication (Roholm, 1938).

In *young rats*, fluorosis leads to generalized osteoporosis or osteomalacia, resembling rickets. The organic matrix and the calcium deposition are irregular. The ossification of the cartilages is retarded; the roentgen transparency of the bones is increased (Bergera, 1927). The bones become much more brittle (Cristiani, 1929; Sutro, 1935). Many guinea pigs with chronic fluoride poisoning show bony hypertrophic deformations of the tibia (Cristiani, 1932). White mice have delayed ossification of the internal ear (A. Lewy, 1928). Fluoride administration to young dogs altered the calcium deposition as in rickets. Long-continued administration led to sclerotic processes with abundant deposition of calcium in "calcium grains" (H. Kellner, 1939). Addition of fluoride to the diet of rachitic *rats* interferes with healing by vitamin D, the new bone being being atypical (Morgareidge and Finn, 1940).

Bones store fluoride, so that *ordinary bone meal* contains 0.04 to 0.05 per cent of F. In industrial chronic fluorosis this rose to 1.3 per cent of the bone ash, 60 times the normal (Roholm), presumably by the replacement of hydroxylapatite by fluorapatite (Huggins, 1937). McClure and Mitchell found abnormal deposition of mineral constituents other than calcium; the total ash is greater than normal and the calcium less than normal.

The *cause of the bone changes* is presumably through interference with the enzyme processes of ossification. Very dilute solutions of fluoride affect the deposition of calcium salts in the matrix profoundly *in vitro*. Monoiodoacetate has similar effects. Phosphatase does not seem to be materially concerned in fluorisis, but De Eds, 1936, reports decreased activity of the bone phosphatase in chronic fluoride poisoning of rats. P. H. Phillips, 1932, reported rise of the plasma phosphatase.

Fluorosis and Scurvy.—P. H. Phillips, 1933, found that guinea pigs receiving fluoride develop a scurvy-like condition on diets containing several times the amount of ascorbic acid which protects normal animals, and the adrenal glands hypertrophy (Phillips and Chang, 1934). Fluoride probably inactivates the enzyme reaction that involves ascorbic acid (Phillips, Stare and Elvehjem, 1934). *Bone marrow* hyperplasia and atrophy and severe *hypochromic anemia* have been reported for long-continued administration to dogs (Roholm, 1937).

Thyroid Relation.—Goldemberg, 1921, reported that rats which received small doses of sodium fluoride (2 or 3 mg. per day for six to eight months) developed marked thyroid hyperplasia, and young rats showed the phenomena of cretinism. Similar effects were observed on rabbits. On this basis he suggested fluorosis as the cause of endemic goiter and cretinism. He also reported, 1930, that fluoride administration decreases the basal metabolic rate of rats and guinea pigs. He concluded that it inactivates thyroxin and used it to treat the thyrotoxicosis of Basedow's disease (1932). Others have failed to confirm these observations: Chaneles, 1929, and Cristiani, 1930 and 1931, obtained little effect on the thyroid structure. Seevers and Braun, 1935, found that fluoride did not prevent the toxic effects of thyroid administration in rabbits, and the histologic picture was the same with or without fluoride treatment. P. H. Phillips, 1926, found that fluoride increased basal metabolism and toxicity of thyroid administration in rats. Schteingart and Sammaptino, 1932, did not observe improvement in Graves' disease. W. May, 1937, however, claims good clinical results, and Kraft and May report that the fluoride level of the plasma in thyrotoxicosis is only half the normal, 0.1 to 0.12 mg. per cent. Rats on subeffective fluoride diet develop fluoride teeth if thyroid is administered. This is not due to increased food consumption, for increase of appetite by insulin does not provoke the tooth changes (R. H. Wilson and De Eds, 1940).

The *thyroid glands store fluorine* much more actively than other organs (Chang, Phillips *et al.*, 1934). R. J. Evans and Phillips, 1938, found the content in hyperthyroidism variable and without relation to the basal metabolic rate, or to the iodine content of the gland. They consider that there is no evidence for any role of fluorine in human thyroid disease.

3-Fluoro-tyrosine is reported to act antagonistically to thyroxin (Litzka, 1936, and Kraft, 1936).

Hyperglycemia is reported to result from intravenous injection of sodium fluoride, 0.5 to 10 mg. per Kg. (Goldemberg, 1928).

Parathyroid Function.—Hauck, Steenbock and Parrons, 1933, found no effects.

Kidneys.—S. Marconi, 1939, reported severe acute parenchymatous nephritis on chronic poisoning of guinea pigs with fairly large doses of fluoride. Others have found chiefly interstitial nephritis, but with degeneration of the tubular epithelium in the severer grades. The histologic changes in the kidneys and thyroids are described by Phillips and Lamb, 1934.

Growth and Nutrition.—Sodium fluoride administered to rats over prolonged periods (Goldemberg, 1917, 1919; Sollmann, 1921; A. R. Lamb, Phillips *et al.*, 1933), in daily doses of 15 to 150 mg. per Kg. of body weight, produces cachexia with progressive impairment of growth and food consumption, but with little mortality, and without histologic lesions. There is also marked interference with estrus and reproduction, but this is secondary to the malnutrition (Lamb *et al.*, 1933). The damage is proportional to the dose, and tends to outlast the administration of the drug; so that the growth of animals poisoned with fluoride remains permanently below that of unpoisoned animals. The diminished food consumption is not due to distaste of fluoride food, for the animals do not prefer unpoisoned food (except with the highest concentrations). The effects are not due to "general salt action," for corresponding doses of NaCl are not harmful. No deleterious effects on growth or food consumption occurred in nine weeks with daily doses, 8 mg. of NaF per Kg. of body weight, or with smaller doses. In rats the malnutrition may be due largely to the deformation of the teeth, which prevents occlusion. However, similar effects from analogous doses have been observed on other animals in which the teeth are not deformed. Cows appear to be more susceptible to the malnutrition than rats, especially during lactation (Phillips, Hart and Bohstedt, 1934). Pigs are less susceptible. Calcium fluoride in the form of "*phosphate rock*" produces the same effects as NaF and in nearly corresponding doses; the chronic fluoride intoxication is, therefore, not due to disturbed calcium balance. The deleterious effect of phosphate rock is not shared by other insoluble Ca salts (phosphate and carbonate) in equal concentration.

Hair growth in rats is retarded by feeding or intraperitoneal injection of fluoride (E. O. Butcher, 1946). S. Spira, 1946, considers the alopecia comparable to thallium poisoning.

Diets low in fluoride (0.05 mg. per Kg. of body weight, daily) do not impair growth. Incisor bleaching begins with 2.5 to 3 mg. (R. J. Evans and Phillips, 1939).

Fluosilicate.—These are generally more soluble than fluorides, except sodium fluoride. Sodium fluosilicate, Na_2SiF_6, is used as a rat poison and has produced fatalities in man. Water converts it partly into NaF and SiF_4, the reaction being favored by alkalinity. Its effects are identical with those of fluoride; indeed quantitatively so, when the dosage is adjusted to the fluorine content. This holds for oral as well as for hypodermic administration (C. W. Muehlberger, 1930). In chronic intoxication by minimal doses, the fluosilicate is the more toxic (Cristiani and Chausse, 1927).

Fluoroacetate of sodium ("Compound 1080") is a highly effective poison for rodents (E. R. Kalmbach, 1945). It occurs in certain poisonous plants of South Africa (C. W. Klingensmith, 1945; see Index).

Gaseous silicon tetrafluoride, SiF_4, is decomposed by the moisture of the air passages into HF and H_2SiF_6, and the latter again into silicic acid, which is precipitated in the air passages (Cameron, 1887).

Organic Fluorides (see Index) are generally less toxic than other halogenated hydrocarbons (Kant, 1933). *Alpha fluoronaphthalene* produces mottled teeth in dogs; fluorobenzene does not (Kempf *et al.*, 1937).

◆

BROMIDES

Fairly large doses of bromides depress the psychic functions and the reflexes, leading to a condition of mental apathy, which conduces to sleep, particularly in nervous insomnia. The bromides are employed to secure sleep, and for sedation in nervous hyperexcitabilities, Graves' disease, hysteria, hyperemesis, cinchonism, and so forth, but their continued use is likely to result in toxic effects, and barbiturates are generally preferred. Their anticonvulsant action is utilized against epilepsy, but they have been largely displaced by phenobarbital and diphenylhydantoin. They generally suppress or mitigate the convulsions, at least in the idiopathic form; but they do not effect a cure. The effects occur slowly and are correspondingly lasting. The administration must be fairly continuous. The action seems to be due to the Br ion as such. It is produced by all the bromides, and to a less degree by the organic bromine compounds. NaBr is generally preferred. The mechanism is not explained. The excretion of Br is analogous to that of Cl. A part is retained persistently. The elimination is hastened by Cl administration; conversely, the Br retention effects are increased by Cl-poor diet. Continued administration of large doses often results in bromide acne, and other symptoms analogous to those of iodism. There may also be considerable psychic depression, malnutrition and lowered resistance. These may contraindicate the use in neurasthenic patients, and the like. Acute bromide poisoning is rare, occurring only after enormous doses. Ordinary doses have no effect on the circulation.

Historical.—Bromine was discovered by Balard, 1826, in sea-water. Its chemical similarity to iodine prompted its trial against glandular swellings, syphilis and thyroid disorders. This was unsuccessful, but led to the observation of its sedative action. Its use in epilepsy is said to date from Laycock, 1853; as hypnotic, from Behrend, 1864. The older literature is reviewed by Krosz, 1876.

Fate.—The organism does not distinguish sharply between the halide and related anions (E. Frey, 1910), which are to a large extent interchangeable; so that the absorption, distribution and excretion of bromide are essentially like those of chloride, iodide, thiocyanate or nitrate. Bromide does not readily penetrate cells, and therefore remains almost exclusively in the extracellular fluids of the body. The renal permeability is somewhat less for bromide than for chloride, and this is less than for iodide.

Absorption.—The bromides are rapidly absorbed from mucous membranes. It was believed that calcium bromide is absorbed more slowly, but Hales and Fishman, 1908, found it excreted at about the same rate as NaBr. In ligated *intestinal segments*, the absorption of bromides is not delayed by the presence of chlorides; but bromide somewhat delays chloride absorption. The lower segments of the small intestine are said to absorb bromide better than the upper (Bolgar, 1910).

Channels of Excretion.—The excretion occurs as bromide mainly by the urine, but with protracted administration, the feces may represent up to a fifth of the total excretion (O. Bodansky and Modell, 1942). Small quantities are also eliminated by the feces, sweat (Tachau, 1911) and other secretions, including the cerebrospinal fluid (Hald, 1911). The amount excreted in the *milk* of a nursing mother who is taking bromide may have a sedative effect on the nursling (Tyson *et al.*, 1938). The excretion of Br by the *sweat* is quite limited. The *epithelium of the skin* may accumulate unlimited quantities of bromide during continued administration, returning gradually to normal when the income is discontinued (Cornbleet, 1938).

The *course of urinary excretion* depends on the total halide concentration of the plasma rather than on the bromide concentration. It starts promptly, but proceeds slowly; *f. i.*, in one to one and one-half days only one-tenth may be excreted, and traces are found after twenty days. The rate is only half or less that of iodides (Herzfeld and Gormidor, 1912). The kidneys are also less permeable to bromides than to chlorides (U. J. Wile, 1923; Hastings *et al.*, 1932). The bromide excretion depends somewhat on diuresis, but only imperfectly (Hales and Fishman, 1908). Salyrgan and theophylline increase the bromide and chloride excretion considerably, sodium sulfate and water very little (O. Bodansky and Modell, 1941). The quantity excreted is proportional to that administered, but always with considerable retention. With continued use, the percentage excreted increases until it equals the ingestion, constituting equilibrium or saturation for that dose. This is reached in about sixteen days (Markwalder). The excretion thus totals one or two-thirds of the amount ingested (O. Bodansky and Modell, 1942). When the administration is stopped, the excretion diminishes, at first rapidly, then more slowly, so that traces may be present for a month or longer. The excretion follows the same course in epileptic as in normal individuals (v. Wyss, 1906).

Chloride administration hastens the elimination of both Br and I (Herzfeld and Gormidor, 1912; Wyss, 1913); Cl-poor foods slow the excretion (Sarvonat and Cremien, 1911). Conversely, the administration of bromides increases the elimination of Cl (Wyss, 1913). Iodide also displaces Br and Cl. Wagner and Bunbury, 1930, reported that the administration of large doses of sodium chloride (15 Gm. three times daily) to patients who had been under bromide treatment actually increased the bromide content of the blood, by mobilizing the tissue bromide faster than it can be excreted. Further studies are desirable.

Bromides on Diuresis.—The urine flow is increased by salt action (Wolf and Opp, 1912).

Bromides in Uranium Edema.—Uranium animals become less edemic when bromides are administered. These cause a greater diuresis; the Cl excretion is as high as normal; and the urine contains a part of the Br. The body therefore loses both water and salt (Leva, 1912).

The distribution of bromide is similar to the normal Cl, which it partly replaces in the blood, gastric juice and other extracellular fluids (Nencki and Simonowski, 1893; Ellinger and Kotake, 1911).

Partition Between Blood Corpuscles and Plasma.—After injections or *in vitro*, the bromide is confined almost exclusively to the serum. A small quantity, however, does go into the corpuscles, more readily than does Cl, so that the Br:Cl ratio is higher in the corpuscles than in the serum (Hastings *et al.*, 1931, 1932). With continued administration, the ratio gradually becomes equalized (M. F. Mason, 1936). The *cerebrospinal fluid*, which has a somewhat higher chloride concentration than the serum, contains distinctly less bromide, if this has been administered by mouth or vein, and eventually even after cisternal injection (Notkin *et al.*, 1936; Wallace and Brodie, 1939, 1940). The ratio for iodide is even lower than that of bromide. The bromide, iodide or thiocyanate content of the plasma must therefore exceed a certain threshold before they pass into the central nervous system.

The *gastric juice* after bromide administration contains a higher bromide concentration than the blood (Quastel and Yates, 1934). Its Br:Cl ratio is the same as that of the blood serum, regardless of the rate of gastric secretion, even when half of the chloride has been replaced by bromide (H. W. Davenport and Fisher, 1940).

The *urine concentration* fluctuates widely (Hastings and Van Dyke, 1931). E. Frey, 1937, claimed that the Br:Cl ratio in the urine is the same as in the serum; and P. K. Smith and Walker, 1938, that it is less than in the serum.

The organ distribution of bromide, iodide and thiocyanate shows approximately the same ratio to chloride as exists in the serum, except in the central nervous system. This appears best explained by the assumption that these ions are confined essentially to the extracellular fluid, since the chloride is almost entirely extracellular (G. B. Wallace and Brodie, 1937). Accordingly the bromide, iodide or thiocyanate content of the organs parallels their content of extracellular fluid. The low bromide:chloride ratio and similarly the low ratios of iodide and thiocyanate of the central nervous system are explained by the fact that these ratios are characteristic of cerebrospinal fluid (G. B. Wallace and Brodie, 1938, 1940; Smith and Walker, 1938). Pathological tissues, tuberculous, syphilitic, tumors, cystic and transudate fluids, all show practically the same bromide (iodide and thiocyanate):chloride ratio as the serum, so that their halides are also extracellular (Wallace and Brodie, 1937). *With long-continued administration*, some of the bromide penetrates the cells, so that its organ distribution is not strictly parallel to the chloride content; but they do tend markedly in the same direction (E. Frey, 1937).

It follows that the *bromide content and concentration of organs* depend on their normal chloride content (Ellinger and Kotake, 1911). Wyss, 1906, found the largest quantity in the blood. Even after long administration, the brain contained a relatively small proportion. The distribution after therapeutic administration is described by Carnot and Coirre, 1914. In a case of acute clinical poisoning, from 100 Gm. of NaBr, the bromide concentration was highest in the blood (E. Vilén, 1926).

The *total volume of extracellular fluid* can be estimated by determining its serum concentration after the administration of a single dose of bromide and making allowance for the excretion. Thiocyanate is also commonly used (Krogh, 1938), but bromide gives better results since its distribution is more uniform. The blood sample is taken three hours or more after the oral administration of sodium bromide, 30 to 50 mg. per Kg. of body weight, the urine being collected during the period (B. B. Brodie *et al.*, 1939). By this method the total extracellular fluid averages 9.7 liters per square meter of body surface for normal males, 9.4 for females (Brodie, Friedman and Ferraro, 1941).

The *normal presence of bromide* depends on the introduction of small quantities in water and food and on occasional medicinal use. Serbescu and Buttu, 1934, found less than 0.1 mg. per 100 cc. of blood in thirty subjects. Ucko, 1936, found between 0.15 and 0.33 mg. per cent, the concentration in the corpuscles being a third of that of the plasma. Normal fasting gastric juice contained 0.5 to 0.9 mg. per cent. The daily excretion was 1.0 to 2.5 mg. The *thyroid gland*, especially if hyperplastic, often has a relatively high bromide content. This is lowered by the administration of iodide or thyroid (E. J. Baumann, Sprinson and Marine, 1941).

Relative Retention of Organic and Inorganic Br.—The organic Br compounds are apparently retained somewhat more efficiently than the inorganic. This has been cited as a proof of superiority; but it is doubtful whether the retained Br is the bearer of the therapeutic action (Magnus-Alsleben, 1911). *Sabromin* is retained more in the adipose tissues, but not in the brain (Ellinger). *Bromipin* is eliminated by the urine, partly in organic combination, but mainly as inorganic bromide (Bermann, 1910. He has also studied the fate of other organic Br compounds). The lipid soluble *bromural* passes at first mainly into the nervous system; but it is rapidly decomposed into a water-soluble form, presumably bromide, which then follows the course of the ordinary bromides (Takeda, 1911). *Tetrabromostearic acid,* which may be ingested by man in quantities of 100 to 150 Gm. without deleterious symptoms, is broken down, the urine containing organically bound bromine (Corley, Tripp and Newton, 1935).

Sulfobromophthalein Sodium, U.S.P., *bromosulphalein,* disodium phenoltetrabromphthaleinsulfonate, leaves the blood stream rapidly after intravenous injection. It is probably taken into the Kupffer and other reticulo-endothelial cells, from these gradually into the polygonal cells of the liver, and then excreted by the bile (A. Cantarow and Wirts, 1941). The rate of its disappearance from the blood stream after intravenous injection is used as a liver-function test (Soffer, 1935, review). Bromosulphalein retention has also been proposed as a measure of the functional activity of the *reticulo-endothelial system.* The retention is increased in dogs by the daily intravenous injection of India ink or ferric oxide (M. A. Mills and Dragstedt, 1936).

Sulfobromophthalein sodium, U.S.P., occurs as a white crystalline powder, very soluble in water. *Sulfobromophthalein Injection,* U.S.P., a watery solution, is usually available in ampuls of 150 mg. in 1 cc. *Average dose,* by vein, 2 mg. per Kg. of body weight.

Roentgenography.—Bromine compounds are nearly as opaque as iodine compounds and are less toxic, less irritant and cheaper. Sodium bromide solution is used especially in the urinary bladder and may be employed in the renal pelvis and ureters (Weld, 1918).

Sedative Action on Man.—A single dose of *1 to 2 Gm.* of sodium bromide is somewhat calming, tends to decrease worry, and inclines to sleep, which is deeper and more dreamful. Conditioned reflexes are slower but truer (Pavlov). Arithmetic performance is improved more than with caffeine, chiefly by decreasing subjective fatigue (Allers, 1929). *Above 4 Gm.,* depression and decrease of reflexes become apparent. The effects are rather different from those of the ordinary hypnotics: the bromides tend to produce a mental calm, aloofness, and imperturbability, progressing to sluggishness, lack of attention and lassitude. These all dispose toward sleep, which it is fairly easy, however, to resist. Perception, observation, and motor reactions may be normal, and the soundness of the mental processes is not impaired, if the effort is made to use them. With the smaller doses the subject awakens refreshed; but with larger doses, the psychic depression persists because of the slow excretion. Very exceptionally (more commonly with cats), bromide causes acute cyclic excitement and mania.

The effects of 5 Gm. of NaBr on the *mental functions* of normal individuals are described in detail by R. F. Stanley and Laird, 1930. The involuntary tonic contraction of skeletal muscles which continues after resistance to the effort is discontinued, is diminished by bromide, little affected by barbiturates, chloral or strychnine, and increased by caffeine (Sapirstein *et al.,* 1936). *Electroencephalograms* show damping of the alpha waves (which are increased in epileptic attacks), indicating cortical depression (H. Berger, 1934).

Still larger doses (*10 to 15 Gm.*) cause some nausea, considerable apathy and confusion of speech, but not sleep (Binz). These doses also lower the reflexes from the skin and mucous membranes, so that irritation of the fauces does not produce retching (Krosz, 1876). This was utilized, before the introduction of local anesthetics, for examinations of the throat, and so forth.

The **central actions of bromides on animals** are analogous to those on man, and can be utilized for studying the mechanism of bromide action.

Experimental neurosis in dogs, produced by confusing conditioned reflexes, is improved within ten days by relatively small doses of bromide. The differentiation of stimuli is reestablished, and the improvement continues to normal after the bromide is discontinued. Alcohol, avertin and barbiturates remove the neurotic inhibition only temporarily, without restoring the differentiation (Petrova, 1934; Dworkin *et al.,* 1936).

Narcotic Actions.—*Rabbits* show both acute and chronic effects closely resembling those observed in man. The symptoms, rapidity and dosage are nearly the same, whether the administration is by mouth, hypodermic or vein (Bernoulli, 1913). Doses of 2.3 to 3.2 Gm. per kilogram, by vein, generally produce little immediate effect After several hours to three days, the rabbit becomes apathetic and sluggish. The sensibility and reflexes are somewhat depressed and delayed. Muscular coordination is often disturbed and ataxic. Ascending muscular debility and pareses are frequent. *Chronic poisoning* also produces these pareses, but no narcosis or other cerebral depressions (Januschke, 1913). Both forms prevent camphor and picrotoxin convulsions. The rabbits often show slowly developing irritant phenomena in the skin and mucous membranes, analogous to bromism: general dermatitis, loss of hair, conjunctival congestion, coryza, and so on. If the acute nervous symptoms are fully developed, spontaneous improvement is exceptional. The rabbits die in coma after several days. *Spontaneous activity of mice* is decreased by single hypodermic doses of 0.2 to 0.6 Gm. of NaBr per Kg., about a sixth of the fatal dose, but within the toxic range. The effect is increased by dividing the dose (Perez-Cirera, 1895). With *guinea pigs,* large doses of NaBr (0.1 to 1 Gm. per pig of 200 to 250 Gm.) produce a deep sleep, lasting two or three days. This is preceded by a long latent period, even if the administration is hypodermic or by vein. The hypnotic effect is antagonized by picrotoxin or strychnine (Januschke and Inaba, 1913). *Cats* receiving 1 Gm. of NaBr per Kg. for three or four days develop cycles of narcosis alternating with excitement. The latter appears analogous to the excitement stage of aliphatic narcosis, and is accentuated by light etherization, abolished by deep ether anesthesia. It does not occur in decerebrated cats, or with rabbits, and but little with dogs (Blume, 1928).

Sedation of Experimental Convulsions.—Albertoni, 1882, found that bromides lower the excitability of the motor cortex of dogs, so that a stimulation of the motor areas which, under the conditions of the experiment, gives rise to general epileptiform convulsions, will, after the administration of a bromide, be confined to the area directly stimulated. The calming effect of bromide renders animals less subject to the "startle reflex," and therefore less liable to *strychnine convulsions;* although the increased primary reflex, for instance the patellar, persists. *Intravenous injection* of sodium bromide suppresses the epileptic convulsions of camphor and the medullary convulsions of cocaine, but not the spinal convulsions of strychnine or picrotoxin (Januschke and Inaba, 1913). The effects of bromide treatment on the response to convulsants were further studied by K. Meyer-Nobel, 1928, and by Boshes, 1934.

The ultimate mechanism of bromide narcosis appears to be a direct effect of the bromide ions, and as these do not readily penetrate into cells, it is presumably exerted on the cell surface. It is not due to deficiency of chloride nor to organic binding of bromide.

The effects are due to the bromide ion. The characteristic action is produced in animals by all bromides, but not by organic Br compounds or by bromates (Januschke, 1913). *The chloride deprivation theory,* suggested by Wyss, 1913, is disproved by the difference of symptoms; for animals remain apparently normal when more than half of their chloride store has been removed in a week, by feeding nitrate with chloride-poor food (Hiatt, 1939). In man, acute chloride deficiency produces tremors, weakness and fever, and not narcosis. Injection of chloride causes some recovery from bromide poisoning; but citrates, sulfates and nitrates have a similar, though weaker, saving action (Bernoulli, 1913). Januschke and Inaba, 1913, found that the bromide depression in animals could not be efficiently antagonized by the administration of NaCl, nor reinforced by Cl-poor food.

Clinical Use of Bromide as Somnifacient.—Bromides enable rather than enforce sleep, by calming excessive restlessness and worry and by quieting pathologic excitability. The dose should be 1 or 2 Gm., or more if necessary, one to two hours before retiring. The bromides may be usefully combined or alternated with the more powerful aliphatic hypnotics. The effect is simply additive (Klammer, 1913), or perhaps slightly potentiated (Januschke and Inaba, 1913). Bromide has little if any action on pain, except that it renders the patient less apprehensive.

Sedation of nervous hyperexcitability is utilized in hysterical conditions, Basedow's disease, acute cerebral excitement, meningitis, the nervous vomiting of seasickness and pregnancy; to prevent cinchonism; against incontinence of urine; as an aphrodisiac in sexual hyperesthesia; against delirium tremens and convulsions—epileptic, chorea and others, and as preanesthetic sedative (0.2 Gm. per Kg., intravenously, thirty-five to forty minutes before the operation; Bréchot, 1932). Barbiturates have largely supplanted all these uses, but bromide is less narcotic and may be useful at least for alternation and potentiation. The dosage for the minor nervous conditions is 0.5 to 1 Gm. two or three times daily; against cinchonism, 3 parts of bromide to 1 of quinine; against seasickness, 4 to 5 Gm. daily for several days before the voyage; in pertussis, it is said to allay the paroxysms, without shortening the course. Convulsions require at least 15 Gm.; if necessary by rectum. Large doses have been given in acute mania, but probably without much benefit.

Psychological performance of healthy human subjects kept on a fixed dosage of bromide for several weeks is not materially affected; if anything, it is improved, except that reaction time is slightly delayed (M. Moore *et al.*, 1942). Large daily doses to dogs increase the volume of *gastric juice,* the free acidity, and the total halogen (I. A. Epshtein, 1939). Bromide treatment does not alter experimental hypertension (H. Goldblatt *et al.*, 1942).

In idiopathic epilepsy bromides produce marked symptomatic improvement in 90 per cent of the patients. Large doses, near the limit of toleration, must be continued for some time. The attacks become milder and less frequent, or may be suppressed entirely; but they usually return soon after the remedy is removed. The rare cases in which the convulsions disappear permanently are presumably spontaneous recoveries. The disadvantages of bromides have led to the partial or complete substitution of phenobarbital, which is at least equally effective. They may be alternated with advantage. Diphenylhydantoin is more potent than either (see Index). The required dose must be ascertained by trial. The efficiency may be increased by Cl-poor food (Ulrich, 1912), or by the administration of calcium (Januschke, 1913). These modifications may succeed when the simple bromide treatment fails. The daily dose of bromide should be divided into three or four fractions, and freely diluted with water. Tablets are undesirable, because of the local salt irritation.

Poulsson recommended the following routine, to be modified as needed: in the first week, 3 Gm. daily; second week, 4 Gm.; increasing by 1 Gm. each week, until 10 Gm. are reached in the eighth week. If well tolerated, and if the attacks persist, the weekly increase may be continued until 15 Gm. are reached in the thirteenth week. The dosage is then reduced in the same way until the attacks recur, when the treatment is again started in the same way. A few trials ascertain the doses required to reduce the attacks to a minimum. This dosage is then continued as long as needed, and renewed at intervals even after complete disappearance of the attacks, to anticipate recurrence. Bromide acne need not interfere with the treatment; but severe depression necessitates reduction, or even discontinuation. The bromide level of the blood should be determined if large doses are used.

Choice of Preparations.—Inorganic bromides are most effective. NaBr is preferred. It is quite as sedative as equivalent doses of the K, NH_4, Ca or Mg bromides (E. Spiegel, 1939); it is less irritant and has a less disagreeable taste than KBr, or especially NH_4Br and LiBr. NH_4Br liberates bromine on exposure to air, which is a serious objection. The long-continued administration, for epilepsy, of large doses of a single bromide would be expected to disturb the cation balance of the body, and a mixture of bromides, such as the "Erlenmeyer Mixture" ($KBr:NaBr:NH_4Br::$-1:2:1) might have advantages. There are no data, however, that this particular ratio is well balanced; and the normal ratio in the body is perhaps sufficiently well maintained by adaptation of the excretion.

$CaBr_2$ adds the depressant action of Ca and is said to be more efficient; but the continued administration of the large quantities of Ca may be detrimental. The same holds probably also for strontium bromide. HBr is too irritant. *Organic Br Compounds* are said to be less likely to produce toxic Br effects; but this could be explained entirely by their low Br content. No real advantage has been established for them, and they are probably much less efficient. No effect can be expected from the bromide in salts which are used in small doses—*e. g.*, bromide of quinine, or arsenic, and so forth. In these it can be useful only by influencing the solubility of dissociability of the compound.

Because of the depressant effects, large doses of bromides should be *avoided* in mental or physical debility, old age, melancholia and neurasthenia.

Gastric Irritation.—Large doses of bromide, especially in concentrated solutions, produce nausea, vomiting and gastralgia, by local salt action.

Acute bromide poisoning is rare, but may occur from large doses, especially if the excretion is imperfect in nephritis. There are mild collapse, impaired speech, stupor and paralytic phenomena. The treatment would be by sodium chloride infusion.

Vilén reports a patient who had taken 100 Gm. of NaBr in the course of thirty-six hours, became deeply unconscious, developed bilateral pneumonia, and died in six days. Blisters formed in the skin.

Bromide rashes ("*bromoderma*") occur frequently, especially on the face, sometimes early, sometimes late, when the administration of bromide is prolonged. They resemble those of iodism. The mucous membranes may also be irritated. Similar effects occur in animals (Bernoulli, 1913). Bromide (or iodide) administration may also cause the "lighting up" of latent inflammatory processes, for instance tuberculosis (Block, 1920). Bromoderma has no direct correlation with the level of bromide in the plasma (Kimberly, 1939). Even acne is generally absent in patients with severe mental symptoms (Gundry, 1939). The rashes are best prevented or treated by cleanliness. They disappear rather slowly after discontinuation.

The *bromide rashes* resemble acne vulgaris (but without comedones). They sometimes become confluent, forming superficial carbuncles. Children are especially susceptible and may show pustules and fleshy masses, distributed symmetrically over the face, trunk and limbs, often becoming confluent and occasionally vegetating (H. MacCormac). An *older explanation* (Adamkiewicz) attributed the bromide and iodide acne to direct irritation by the liberation of free bromine or iodine by the acid secretions of the sebaceous glands, and the like. This cannot be accepted (Unna, 1912), for these elements could not exist free at the reaction of the body. Bromide administration sensitizes to the "*luetin*" *test*, although less actively than iodide (Cole and Paryzek, 1917; Kolmer, 1917).

Chronic Bromide Depression, Psychosis and Cachexia.—Long-continued use generally leads to psychic deterioration, weak memory for recent events, apathy, somnolence, unequal pupils commonly widely dilated; thick and unintelligible speech; coarse tremors of the lips and hands; ataxia, diminished deep reflexes; loss of sensitivity to touch and pain; tenderness of the calf muscles; sexual impotence; and to nutritional disturbances: anorexia, fetid breath, coated tongue; malnutrition, anemia, emaciation, diarrhea, often fever of 100° to 103° F., tachycardia of 120 to 140 and lowered resistance. The symptoms disappear fairly rapidly when the drug is stopped or the dose reduced, and especially if 6 to 8 Gm. of sodium chloride are taken daily (Schabelitz, 1916); but the resistance remains low for some time. With persistent intensive administration, *serious psychic phenomena* develop, colored by the personality of the patient (Diethelm, 1930); beginning with restlessness and disorientation, followed by paranoid trends, hallucinations, apprehensions, delirium, finally stupor and coma. Many cases are caused by failure to recognize the symptoms (W. Sensenbach, 1944). The paranoid schizophrenia usually clears fairly soon after withdrawing the bromide (M. Levin, 1946).

The *relation between bromide concentration and symptoms* is fairly close in a given patient subjected to intensive bromide treatment, but differs considerably for individuals. In general, 50 to 150 mg. of Br per 100 cc. of serum corresponds to some confusion; 150 to 250 mg. to incoordination and emotional outbursts; about 200 mg., toxic psychosis; concentrations about 300 mg. are dangerous to life. On discontinuing the administration, the blood concentration falls slowly, at the rate of about one-half per month (C. P. Wagner and Bunbury, 1930; L. P. Gundry, 1939; Sharpe, 1934). The mental symptoms often respond more slowly to withdrawal than does the blood bromide level. A clinical method for determining the bromide concentration was described by O. Wuth, 1927 (J.A.M.A., *88:* 2013). *The chloride concentration* of the plasma decreases as the bromide rises. It has generally fallen 25 to 30 per cent, when intoxication symptoms appear; more than 40 per cent of fall is generally fatal (Bernouilli, 1917).

Bromide administration to pregnant rats, throughout gestation, reduced the maze-learning ability of the offspring, although these had a normal bromide content at the time (B. K. Harned *et al.*, 1944).

Nutrition.—Bromine does not appear to be an essential element; rats on a diet as Br free as possible grew as well as those fed on ordinary food (Winunek and Smith, 1937).

Bromides on General Metabolism.—The actions are not important (Chittenden, 1884; Jappelli, 1913).

Muscle respiration and contraction are affected by sodium monobromoacetate in the same manner as by monoiodoacetate—indeed, the characteristic muscular effects were first described by J. Pohl, 1888, for the bromoacetate. He reported that small doses administered to frogs produce muscular stiffness and fibrillation, terminating in contracture, while the heart was still beating, although this was also killed eventually. He showed that the effect is not prevented by curare, but that it does not occur if the nerve is divided, unless it is stimulated. The action is therefore a modified peripheral response to fatigue. Mono- and dichloroacetate caused less of this effect; trichloroacetate, none. He also investigated a number of other substituted fatty acids, and pointed out the difficulty of correlating these actions with the chemical constitution. Sodium bromide itself tends to produce muscular contracture, iodide more so, and thiocyanate still more (Gasser, review).

Actions on Circulation.—Bromide has no effect, except slight depression with single doses above 10 Gm. Sedative doses may indirectly slow the heart and lower the blood pressure somewhat, especially in cardiac neuroses. Larger doses of KBr may show the depressant potassium action.

In the cat, the *intravenous injection* of the NaBr, 3 cc. of 1.5 per cent per kilogram, had no effect (Lehndorff, 1914). In *perfused hearts,* the substitution of bromides for chlorides in Ringer's fluid produces practically no effect in cold-blooded hearts, except a slight acceleration in starting. In warm-blooded hearts, there was a slight decrease in rate and amplitude (Greene and Kruse, 1913).

In *perfusion of isolated respiratory center,* this is stimulated with iodide, bromide and nitrate ions (Macht and Hooker, 1918). The conditions and concentrations, however, are too artificial for practical application.

Excised Uterus.—Replacement of Cl by Br or I produces a slight increase of tonus, without affecting the rhythmic contractions. Fluoride increases the tonus and rhythmic contractions, without injuring the muscle (Prochnow, 1911).

With **isolated intestine** and other smooth muscle, the replacement of the chloride of Ringer's solution by bromide increased the tone, amplitude, rate and rhythmic excitability, especially in mammals (T. K. Kruse, 1917).

Secretions.—Bromide somewhat increases the secretion of mucus by salt action. It diminishes the milk. Variable results have been reported as to menstruation.

PREPARATIONS.—***Sodium Bromide,** U.S.P.; NaBr; occurs as colorless, cubical crystals or white granular powder; odorless; saline taste. Freely sol. in water (1:1.2); sol. in alc. (1:16). All bromides are *incompatible* with strychnine. Average dose, 1 Gm., 15 grains. *Potassium Bromide,* U.S.P., freely sol. in water (1:1.5).

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IODINE, IODIDES AND THYROXIN

These may be discussed together, since all iodine compounds have features in common. All are convertible into thyroxin, and in this manner affect metabolism and the associated phenomena in thyroid disease. Those which can be administered in relatively large doses, and presumably give rise to iodide ions, produce iodism, and characteristic inflammatory reactions in syphilitic and other pathologic formations. The inorganic iodides exert osmotic and other indifferent "salt actions." Elementary iodine is eventually converted into iodide, but first combines locally with the proteins of the cells and is irritant and antiseptic.

Historical.—Iodine was discovered in 1811 by Courtois, was studied by Gay-Lussac, 1813, and by Humphry Davy, about the same period. Its effects were investigated by Vulpian and his pupil Magendie. The latter's "Formulaire" of 1824 contains fairly comprehensive data. It was introduced into medicine by J. J. Coindet of Geneva, in 1820, for the treatment of goiter. It aroused considerable enthusiasm, and its use was extended to other diseases. Berton, 1829, advocated the inhalation of the nascent fumes. The occurrence of mishaps brought it into disrepute, and the resulting abuse greatly embittered Coindet's life. Coindet, in 1820, proposed the use of iodide of mercury in "venereal affections complicated with scrofula," and this was employed by Biett, 1821, in the treatment of syphilides. Effective therapy of tertiary lesions with iodine was first reported by Lugol, 1831, but the credit of establishing its usefulness is generally given to William Wallace of Dublin, who published in 1836 a series of cases treated with effective doses of potassium iodide (2 Gm. three times daily). Its employment spread rapidly, especially through the authority of Ricord. The use of iodine as a surgical antiseptic appears to have originated with Boinet, 1839, who treated an inguinal abscess with injection of a diluted tincture of iodine, and then used it also against infection of the vagina and the skin; shortly after he introduced the injection of the tincture into ovarian cysts. Iodine for goiter prophylaxis was proposed by Chatin in 1850. Medicinal qualities of iodine were known long before the element was isolated. In the thirteenth century, Arnold of Villanova described the use of "*Burnt Sponge*" in "scrophula," which probably covered goiter and perhaps even syphilis. This carbonized sponge contained ½ to 3 per cent of sodium iodide and its dosage of 1 to 3 drachms therefore contained 0.06 to 0.4 Gm., 1 to 6 grains of NaI. The origin of this use is not known, but a Chinese codex of 1567 B.C. is said to advise seaplants against goiter. *Cod liver oil* also contains iodine, from 3.6 to 14.9 mg. per liter (A. D. Holmes and Remington, 1935). The usual daily dose of 10 cc. averages about 0.085 mg.

IODINE

Elementary iodine precipitates proteins, the iodine being partly adsorbed, partly loosely bound and partly converted into iodide ions. This precipitation causes persistent irritation, usually short of corrosion. Since the iodine itself is but loosely bound, it continues to penetrate, so that the action extends deeply. It may be conveniently graduated by successive applications of the alcoholic or watery solutions. The official tinctures and the "strong solution" (Lugol's solution) contain potassium iodide to make them more stable and more miscible with water. Iodine ointments give up their iodine slowly, so that their action is milder. A part of the iodine is chemically combined with the base—all, in some proprietary ointments—so that it cannot react with the proteins, and is therefore ineffective.

Local Phenomena.—Applied to the skin, iodine produces a mahogany stain, smarting, erythematous inflammation, infiltration of subcutaneous tissue, desquamation of the epidermis in large shreds; if repeated, vesication results. The effects on mucous membranes are more severe and may produce corrosion. Its action is chemical, since it precipitates proteins as easily dissociated compounds. It is absorbed somewhat from the skin and excreted mainly in the urine as iodide. Iodine is used as *counterirritant*, especially in chronic pleural effusions, chronic rheumatism, diseased joints, enlarged lymph glands, lymphangitis, and so forth. It has also been employed in erysipelas, painting the tincture from the periphery toward the center, five or six times daily (Ferrari, 1911), but Wood warns that the action must be graded very mildly, or it will produce extensive necrosis.

The "*absorptive*" *effect* of iodine was demonstrated experimentally on the fibrous nodules following intradermic injection of local anesthetics (Sollmann, 1919). Positive results were obtained only if the iodine was applied daily for eight days, and pushed to considerable irritation of the skin. Shorter continuance was ineffective, even if a larger amount of iodine was applied and the irritation was more intense. *Injections into cysts*, hydrocele, empyema, and the like, produce at first increase of the fluid, then adhesive inflammation. The injections are painful, and have often caused serious poisoning. They have been displaced by surgical procedures.

Severe injury to the female genito-urinary tract has followed intra-uterine injection of iodine solution.

In rabbits and guinea pigs, repeated injections resulted in inflammatory reactions, ranging from endometritis to cysts of the uterine horns and tubes, by occlusion of the abdominal end; and in degenerative changes of the ovaries, their degree depending on the duration of the treatment, rather than on the amount injected (Sodano, 1934).

The **antiseptic action of iodine** is used to *prepare the skin for operations* (introduced by A. Grossich, 1908, 1910). A 3 per cent alcoholic solution is painted over the dried skin of the operative field on the preceding day, and again just before operating. This is preferable to the official tinctures, since the potassium iodide of the latter delays drying and penetration. There may be rather severe irritation (Herzog, 1914). R. A. MacDonald and Peck, 1928, recommended a 1.25 per cent solution in 70 per cent isopropyl alcohol. The stain may be removed by warm concentrated solution of sodium thiosulfate (Snoy, 1911) or by ammonia. The value of iodine for *wound disinfection* is in dispute, on the basis that the tissue injury may more than offset the antiseptic action. It may be used as the official tincture, or better the official Iodine Solution.

Streptococci in *cultures* are destroyed by iodine, 1:1000, in one-fourth of a minute, even in moderately albuminous fluids (Albert and Taylor, 1918). Experimental results with *infected wounds* were also good, the iodine being effective within five hours after injection, *i.e.*, until the bacteria have spread too deeply (Brunner, 1915). On the other hand, bacterial tests from the *skin* after iodine application have given questionable results. Experiments with *tissue cultures* show that iodine is rather more toxic to bacteria than to human connective tissue cells. It tends to dissolve the fibrin of the cultures (R. A. Lambert, 1916). *Spirochete cultures* are not especially susceptible to iodine; the fatal concentration is 1:75 in KI solution (Akatsu, 1917).

Against *tinea capitis*, the Iodine Tincture, N. F. (2 per cent), may be dabbed on morning and night, or a 10 per cent ointment in adeps lanae, suspending the applications if the reaction becomes severe (Wise and Wolf, 1936).

Individual water sterilization may be effected by the "*Violle and Seigneurin mixture*," a powder added to the water in the ratio of 60 mg. of iodide, 30 mg. of iodate, 3 mg. of potassium permanganate and 60 mg. of citric acid. This secures an iodine concentration of 12 ppm, which destroys intestinal bacteria in about twenty minutes. It is more effective and more stable than Halazone, but has a slight iodine odor and color.

Tablets of *triglycine hydroperiodide* for individual water canteen purification are reported superior to the chlorine type (J.A.M.A., *132*:930, 1946).

Iodine Against Burns.—A 10 per cent tincture has been used. It causes severe pains for four or five minutes, said to be succeeded by complete relief of pain (Mercier, 1919), presumably owing to a precipitation pellicle. The advantage of iodine over other astringents is doubtful; the irritation and systemic effects may be harmful.

Pharmaceutic Preparations.—Simple alcoholic solution of iodine spreads more evenly and coagulates protein more rapidly. These are advantages in skin infections. The skin should be dry, to avoid precipitation of the iodine. The presence of KI, as in the official Tincture, and in Compound Solution, delays precipitation and favors penetration, and is therefore better for wound disinfection. It is not more irritant to the skin. The presence of an iodide is essential if the iodine is to be diluted with water. It also retards the formation of HI in the tincture. In watery solutions, a minimal iodide-iodine ratio favors adsorption and therefore gives a maximal surface activity (Karns *et al.*, 1932). Some proprietary "soluble iodines" use HI in place of KI. This has no advantage, either as to efficiency or irritation (Sollmann, 1919).

"*Starch Iodide*," the blue adsorption product of iodine and starch, combines slowly with protein and is but slightly irritant. Starch containing 1 per cent of iodine has been used as an antiseptic wound dressing (Luncere, 1917).

Toxicology.—If iodine or its solutions are swallowed, the *symptoms* develop in the order: gastric uneasiness, disagreeable metallic taste; vomiting; violent abdominal pain; severe collapse with feeble pulse; diarrheic stools, sometimes bloody. Severe cases may develop hemorrhagic nephritis. The collapse may be postponed to the second day. The vomit has the color of iodine, or is blue if starch is present. Extensive application to the skin sometimes produces nervous phenomena and fever. *The treatment of iodine poisoning* consists in evacuation; demulcents (eggs, milk, oils and cooked flour or starch, which form loose compounds with iodine); dilute alkalis ($NaHCO_3$); and 5 per cent sodium thiosulfate ("Hypo"). This binds the iodine: $2Na_2S_2O_3 + 2I = 2NaI + Na_2S_4O_6$ (Sabbatani, 1913). The further treatment is symptomatic. The *prognosis* is generally favorable; but Velpeau recorded thirty deaths, in 130 cases. Iodine tincture caused four suicidal deaths in New York City in 1937. *The fatal dose* is usually to about 2 or 3 Gm.; but recovery is said to have occurred after 10 Gm.

Toxic effects from iodine absorption from cysts consist in cyanosis, salivation, vomiting, skin eruptions, high fever and collapse. The urine is scanty and albuminous. The intoxication may persist for several days and then end with sudden death.

Toxicity of Iodine Fumes.—The inhalation of iodine vapor produces pulmonary irritation (dyspnea, and so forth). The inhalation of more than 18 mg. per Kg. is fatal. The danger is increased by the presence of respiratory disease, bronchitis, and the like. This should enjoin caution in the therapeutic use of iodine inhalations. The iodine is partly absorbed, appears promptly in the urine and produces histologic changes in the thyroid (Luckhardt *et al.*, 1920).

Intravenous Injection of Iodine.—Boehm, 1876, found that 0.04 Gm. per Kg. was fatal. Symptoms set in only after six or eight hours, with exhaustion, dyspnea and death in twelve to twenty-four hours. Necropsy showed bloody pulmonary and pleural exudate and renal congestion and hemorrhages. Salant and Livingston, 1916, reported that the intravenous injection of iodine depresses the circulation greatly in cats, not in dogs.

Local Action of Iodine on the Heart.—Perfusion of excised frog hearts with dilute iodine solutions produces irregularities, followed by depression. Stronger solutions result in diastolic arrest.

PREPARATIONS.—*Iodine*, U.S.P. (Iodum); occurs as bluish-black, friable scales, of distinctive odor and acrid taste. Slightly sol. in water (1:3000); sol. in alc. (1:13) or glyc. (1:80); freely sol. in fat solvents or aqueous solutions of iodides. Its solutions are *incompatible* with alkaloids, alkalis, carbonates, tannic acid, turpentine and volatile oils. *Strong Solution of Iodine*, U.S.P. (*Lugol Solution; Compound Solution Iodine*), contains 5 per cent iodine, 10 per cent KI, in water. Average dose, 0.3 cc., 5 minims. ***Tincture of Iodine, U.S.P. XIII, is a solution of 2 per cent of iodine and 2.4 per cent of NaI, in** diluted alcohol. The "Tincture of Iodine" of the U.S.P. XII was a stronger preparation, containing 7 per cent iodine and 5 per cent KI in diluted alcohol. This is now official as *Strong Iodine Tincture*, N.F. VIII. The iodide in the tincture makes it miscible with water and insures against loss of strength on keeping (Wetterstroen, 1908). When iodine is administered in milk, it is largely converted into iodide and albuminates. *Iodine Ointment*, N.F., has 4 per cent each of iodine and KI, in glycerin and yellow ointment. When free iodine is rubbed with fat, it combines almost immediately and completely; but when KI and glycerin are added, as in the official ointment, this combination is restricted; these ointments contain permanently about 3 per cent of free iodine (Warren, 1917). The most stable ointment is made with yellow petrolatum (Ewe, 1920). Iodine is soluble in *liquid petrolatum* to 1.4 per cent, practically without combination (A. M. Clark, 1919).

IODOFORM

This is obtained by the action of iodine on alcohol or acetone, in the presence of alkalis. It has been known since 1832 and was introduced as antiseptic about 1879. It came into extensive use as a dusting powder, especially to promote granulation and to diminish infection of open wounds. It was also injected into tuberculous joints, usually as an emulsion with glycerin (iodoform 10, alcohol and glycerin each 45). It has been practically abandoned because of its *disadvantages*, especially the persistent odor, which cannot be disguised by any perfume. Iodoform is also liable to develop iodism and irritant phenomena in susceptible individuals, producing particularly *eczemas*, even in minute amounts. It may cause severe poisoning with narcotic symptoms, different from those of other iodides.

Iodoform itself is practically insoluble and probably inactive. It is also quite stable outside of the body; but in contact with tissues or their extracts, and particularly with diseased tissues and with bacteria, it slowly *evolves iodine* (Altenburg, Schmidt, 1901). This occurs so slowly that the effects are mild, but somewhat antiseptic to bacteria and stimulant to the cells. It dries the wound secretions and is mildly hemostatic and analgesic. Hamburger found that it stimulated phagocytosis. Its injection into dogs leads to persistent leukocytosis (W. Weil, 1913).

General intoxication may occur when iodoform is applied over a large area, or when it is injected. The symptoms are diuresis, nausea and anorexia, lassitude and somnolence, headache, confusion, apathy or marked irritability, striking pallor, hallucinations, diminished reflexes, light convulsions and paralyses. The temperature rises, then falls. Death occurs through general paralysis of the central nervous system (M. Grossman, 1920). Sodium bicarbonate is said to be antidotal. *Chronic poisoning* is also characterized by paralytic phenomena. The heart, liver and kidneys exhibit fatty changes. Iodoform dermatitis is sometimes seen. It resembles ivy poisoning (Bryan, 1903). The idiosyncrasies cannot be transferred passively (Stropeni, 1912). Fatal poisoning from intrapleural injection is reported by v. Bonsdorff, 1916.

Excretion.—Iodoform is not excreted as such. It appears in the urine as iodide and iodate, and as unknown organic compounds (Angliolani, 1903).

Iodoform (Triiodomethane), CHI_3, contains 97 per cent of iodine. Usually obtained by the action of iodine upon alcohol or acetone, in the presence of an alkali. Fine, lemon-yellow powder or crystals; peculiar, very penetrating and persistent odor; unpleasant, slightly sweetish taste suggestive of iodine. Nearly insol. in water; sol. in alc. (1:60), in glyc. (1:80) or olive oil (1:34); freely sol. in eth. (1:7.5). Dose, 0.03 to 0.2 Gm., ½ to 3 grains, in pills or capsules. Iodoform (and other loose iodine derivatives) are *incompatible with starch.* They are generally *decomposed by heat*, and can therefore not be sterilized in this manner. Since they become antiseptic when applied to wounds, sterilization is usually superfluous. "*B.I.P.P.*" (Bismuth-iodoform-petrolatum paste), an ointment used as a dressing for infected wounds, is a mixture of one part of bismuth subnitrate and two parts of iodoform, with sufficient liquid petrolatum to make a paste (Morison, 1916). A similar mixture was used by Calandra, in 1908.

Iodoform Substitutes.—A number of odorless iodine derivatives were tried, especially *thymol iodide* (*aristol*), but they do not seem to have the peculiar activity of iodoform. They are all insol. in water, and, like iodoform, injured by light and heat.

Thymol Iodide, U.S.P. (Dithymol-diiodide; Aristol); a mixture of iodine derivatives of thymol. Insoluble in water, readily soluble in fat solvents. Chocolate-colored powder with slight aromatic odor

Iodochloroxyquinoline (Vioform) is now used chiefly as amebicide (see Index). It is administered in capsules, 0.25 Gm. three times daily for ten days; the course may be repeated after ten days of intermission. This dosage does not produce irritation or other untoward symptoms. The lethal dose for rabbits, 0.25 Gm. per Kg., injures the liver. In man, it is rapidly excreted by the urine (C. D. Leake, 1931).

IODIDES

The behavior of the iodides in the body is similar to that of the corresponding chlorides and bromides. The immediate toxicity is low, even with intravenous injections, although these disturb the colloidal equilibrium more profoundly than sodium chloride solution. The acute reactions that occur during or shortly after such injections are salt-colloidal. The special iodide reactions which are more toxic occur later and will be described under iodism. The distribution and excretion of the iodides is similar to that of the chlorides and bromides, except for the affinity for the thyroid gland. Like other neutral salts, the iodides are diuretic and expectorant. Salt action plays a part in these effects; but other factors cooperate at least in the expectorant action. *In vitro*, iodides tend to render colloids more soluble and less viscid. It is doubtful whether this occurs with the concentrations reached therapeutically. The effect on the thyroid gland is considered under that heading.

Expectorant Action.—Iodides increase the secretion of bronchial mucus and render it less viscid; they are therefore used in cough and especially in chronic asthma (H. M. Carryer *et al.*, 1946). The secretion may be partly a reflex from the peculiar saline taste that is excited by the secretion of the iodides in the saliva and mucus.

The amount of fluid collectable from the respiratory tract of cats and rabbits is increased by potassium iodide, not by iodized fats or proteins. The increase is a gastric reflex; there is no evidence of any direct effect on the bronchial glands (E. M. Boyd *et al.*, 1945).

However, there may be a more direct effect, for E. J. Stieglitz, 1923, found by histochemical methods that the free borders of the bronchial and tracheal epithelium become especially rich in iodides. Gordonoff and Lehmann, 1936, report that intravenous injection of potassium iodide secures a higher and more prolonged blood sugar rise when isotonic dextrose solution has been injected into the bronchial tree.

The *secretion of saliva* is not normally affected by iodide administration (V. E. Henderson, 1910); but inflammation of the parotid gland is one of the phenomena of iodism.

Urine Flow.—Iodides have a saline diuretic action somewhat greater than that of chlorides, because they are not reabsorbed so well from the urinary tubules.

Lactation is increased by small doses of iodide, as to volume and the percentage as well the total fat. Larger doses, pushed to cachexia, arrest lactation in women and in animals (bibliography, Scharrer).

The *acute effects of intravenous injections of sodium iodide* are practically important because it has been proposed to administer the drug clinically in this manner. The immediate toxicity is not very high. Weld, 1918, for instance, observed no acute toxic effects in dogs with 8 cc. of 25 per cent per Kg., *i. e.*, 2 Gm. of NaI per Kg.; but 0.8 Gm. per Kg. is followed in one-half to one and one-half days by edemas and nervous phenomena, often fatal (see below). Clinically, 5 to 20 Gm. of NaI as 20 per cent solution are injected slowly; symptoms arise when 10 Gm. (about 0.15 Gm. per Kg.) are exceeded. Up to this dosage it is said to be generally safe (E. D. Osborne, 1922). However, the possibility of undesirable changes in blood colloids (increased sedimentation rate; Hanzlik *et al.*, 1925) should be borne in mind. As the iodides are absorbed rapidly and completely there seems no reasonable justification for intravenous administrations, unless, indeed, the colloidal "reactions" are desired, and not the iodide effects. This is probably the mechanism of the rapid relief of herpes zoster, reported to occur after four intravenous injections of 20 cc. of 10 per cent sodium iodide (Reynolds). Before injecting iodide intravenously, the patient should be tested for the absence of exaggerated susceptibility, by administering by mouth, 1 Gm. three times a day, for two days (Osborne).

Delayed Toxicity of Intravenous Injections; Iodide Edema.—Large doses (0.8 Gm. of NaI per kilogram) produced death in twelve to thirty-six hours, with symptoms of central paralysis. Autopsy shows pleural exudation, often with pulmonary edema and pericardial effusion (Boehm, 1876; Chiari and Januschke, 1910). Serous effusions develop in about 30 per cent of dogs with 0.5 Gm. of NaI per Kg.; with 0.8 Gm., 75 per cent develop the effusion (Chu and How, 1931). Similar effects are produced with hypodermic, but not with oral administration (Sgalitzer, 1908). The symptoms are complex, and the statements regarding central actions are contradictory and probably untrustworthy (Jodlbauer, 1902). Intravenous injection is said to paralyze the *vagus endings* and to lower the excitability of the *depressor*. The *perfused respiratory center* is stimulated by iodide, bromide and nitrate ions (Macht and Hooker, 1918).

Use in Circulatory Diseases.—Iodides are employed in arteriosclerosis, coronary sclerosis, angina pectoris, aortic aneurysm (Bouillaud, 1858), and the like. In the lighter grades of these conditions their continued administration seems to give gradual relief to the functional phenomena, especially the pain. The effects are not due to any change in the blood pressure, but probably to structural alterations in the vessel walls, perhaps absorption of cellular exudates; analogous to the effect on syphilis. In many cases a syphilitic factor is directly concerned. In some cases they may be effective by correcting the circulatory erethismus of hyperthyroidism (McEachern and Baker, 1930). They may also cause general lassitude as do thiocyanates.

Direct Action on Circulation.—Potain and others supposed that the iodides lower blood pressure by depressing the heart or blood vessels. This applies to fatal doses of

KI, but is then a potassium effect. Ordinary doses have no effect on the blood pressure in normal men or animals (Stockman and Charteris, 1901). Salant and Livingston, 1916, observed no effects on the circulation of frogs or mammals, even with fairly high concentrations of NaI. The blood pressure *in arterial hypertonus* is also unaffected acutely, and probably even with continued administration (Hewlett, 1912). On the other hand, some clinicians claim a definite fall (*f. i.*, Rutkewitch, 2 Gm. daily). There is also a fall in lead poisoning, probably indirect (Capps, 1912). Guerwitsch, 1907, frequently observed increase of pulse rate with iodide administration. This may have been a thyroid effect.

Isolated Heart and Arteries.—Macht, 1914, investigated the effects of replacing part of the NaCl of Locke's solution by NaI or KCl. The results cannot be transferred to intact animals or man, since they involve different concentrations. Guggenheimer and Fisher, 1927, reported that 0.00002 per cent of iodide in the perfusion fluid dilates the vessels. Mancke, 1930, failed to confirm the claim of coronary vasodilatation of the perfused heart.

Decreased Viscosity.—Iodides and thiocyanates decrease the viscosity of colloids (Pauli, 1903; the other haloid ions have a similar but weaker effect; Gazzeti, 1913). O. Mueller and Inada, 1904, claimed diminished viscosity of the blood from therapeutic doses and advanced this as an explanation of the circulatory effect, but it was not confirmed by subsequent workers (Partunier, 1917, and others).

Epinephrine Atheroma.—Koranyi, 1906, claimed that this could be prevented by iodides, but this has been disproved (Hedinger and Loeb, 1907). *Cholesterol aortic sclerosis* of rabbits is probably promoted by potassium iodide or organic iodine compounds, for they cause a marked increase by the cholesterol level of the liver and blood over that produced by cholesterol feeding alone; decreased cholesterol in the bile; and more marked lipid deposits in the aorta (S. R. Rosenthal, 1934).

Skeletal muscle develops contracture, rigor and acidity on immersion in isotonic iodide solution, or by injecting it into frogs (Stockman and Charteris, 1901; review, Gasser).

Metabolism of Normal Individuals.—In the absence of thyroid disease, administration of clinical doses of iodide does not alter the basal metabolism. The urinary nitrogen may be increased, and with KI (1 Gm. per day) the nonprotein nitrogen of the blood may rise 30 per cent, although the phthalein excretion remains normal (Grabfield *et al.*, 1923). Some increase of urea, total nitrogen, uric acid, purine bases and chloride excretion was reported by Chistoni, 1911. In rats, administration of more than 0.5 mg. of KI lowers the metabolic rate (Hildebrand, 1933). Hypodermic injection of large doses may produce no effect or considerable increase or decrease of metabolism (Sgalitzer, 1908).

Nutrition and Growth.—Long-continued use of large doses of iodides leads to the malnutrition described under iodism. Small amounts of iodide slightly increase the body weight of *rats* (Hanzlik, Talbot and Gibson, 1923; review of iodide on nutrition, Orr and Lutch, 1929). Oral administration of 0.1 Gm. of KI per day to *adult rabbits* causes marked loss of weight, with terminal cachexia, diarrhea and rise of temperature, similar to the effects of bromide cachexia in man. Postmortem examination shows enlarged adrenals; and pulmonary hyperemia and pleural effusion in many of the animals. *Growing rabbits* appear to be more tolerant: 0.5 Gm. per Kg. orally does not appreciably alter the rate of growth, but produces marked tolerance, so that no effects follow doses that would be fatal to the nonhabituated. Excessive doses cause flaccidity and paralysis of the skeletal muscles, especially in the hind legs (Westra, 1934).

Sexual Functions.—Iodides are said to increase menstruation, to decrease the secretion of milk, and to cause atrophy of the mammary gland. Free iodine or loose iodine compounds (not KI) produce sterility in both sexes in rabbits. The spermatoblasts show histologic changes, and the formed spermatozoa are also affected (L. Adler, 1914). It has not been demonstrated that this occurs in the therapeutic use.

Absorbent and Alterative Effects.—Iodides are administered in a variety of obscure conditions to mobilize fibrous tissue, or to alter the general disposition in the direction of health. The vagueness of these conceptions express the vagueness of the expected effects. So far as they exist, they may be analogous to iodism; not infrequently they include a syphilitic factor. These uses comprise: the absorption of nonluetic hyperplastic tissue; of fibroses and other chronic inflammatory lymphatic swellings; gout and chronic rheumatism; neuralgias; asthma, and so forth. The action on bronchial muscle is doubtful (Titone, 1913).

Chronic poisoning by lead, mercury and other metals is treated with potassium or sodium iodide, with the hope of promoting the excretion of the stored metal by converting it into more soluble compounds. There is little direct evidence for this, although there are some chemical data for lead which point in this direction. The appearance of stippled cells after iodide treatment is not distinctive (J. Bohm and Fellinger, 1936).

Iodism.—If the administration of iodine compounds is continued beyond a certain amount, which varies for different individuals, irritative phenomena tend to develop in the skin and in mucous membranes. These are quite distinct from the local action of iodine, or the ordinary salt action of iodides, or from thyroxin actions. Iodism tends to light up certain sluggish inflammatory processes, such as tuberculous and gummatous lesions, and to sensitize the skin to the injection of agar solutions. It appears quite probable that iodism consists in the unmasking of latent inflammations or subthreshold irritations. However, this intensifying effect has been demonstrated only for a few types of irritation. The provocation of this acute inflammatory reaction is also the most plausible explanation of the therapeutic effect of iodides in syphilis and other interstitial inflammations. Phenomena analogous to those of iodism are produced by bromides, nitrates and thiocyanates. Thiocyanates produce similar therapeutic effects; bromides and nitrates have not been used successfully for these actions, but the difference may be merely quantitative.

Phenomena of Iodism.—The irritations take the form of various rashes, and of coryza, headache, conjunctivitis, laryngitis, bronchitis, the various manifestations of a "cold." Less common are stomatitis, parotitis, anorexia. The skin affections generally occur somewhat later. They may consist in acne, furuncles, erythema, purpura, urticaria or vesication, and may be accompanied by fever. The lesions sometimes resemble gummas. The *susceptibility* to these irritations varies greatly. They may set in a few hours after a relatively small dose or only after the long-continued use of large doses; or the symptoms produced by small doses may disappear when the dosage is increased. They disappear in a few days when the drug is discontinued. They may be produced by any iodine compound, but probably only after the dissociation of the iodide ion. Continued administration of iodide may also lead to *iodide cachexia*, anemia, emaciation, lowered tone, mental depression, nervousness, insomnia, nervous tachycardia, sexual impotence.

Agar and Luetin Reaction.—The intradermal injection of agar or starch solution, or of "luetin" which contains agar, produces only temporary wheals in the skin of normal individuals; but if it has been preceded by the administration of a sufficient amount of iodine compounds, there is a much more marked nodular or pustular reaction (Stokes, 1917). Bromides and nitrates also provoke the reaction, but not so powerfully (Cole and Paryzek, 1917; Kolmer *et al.*, 1917).

The *mechanism of iodism* is not due to the liberation of free iodine, nor to anaphylaxis in the ordinary sense.

Iodism was formerly attributed to the *liberation of free iodine* by carbonic acid (Binz, 1875), but this is incorrect, since elementary iodine could not be liberated under the conditions of the body; moreover, entirely similar phenomena are produced by thiocyanates, from which no chemical irritant could be liberated. Nor is iodism due to an *anaphylaxis* in the ordinary sense, for the skin of iodism or bromism patients is not hypersensitive to the intradermal injection of iodides or bromides (Wile, 1921); nor does the serum of iodism patients, when injected into guinea pigs, render these hypersusceptible (Cole, 1911), as had been claimed (Bruck, 1909; Klausner, 1910). Serum treated with free iodine *in vitro* has rather peculiar anaphylactic relations, for its injection leads to the production of a universal, *i. e.*, nonspecific, serum precipitin (Obermeyer and Pick, 1904), and also to a hypersensitivity to iodine injection (Friedberger and Ito); but artificially iodized serum is not comparable with the administration of iodide. Several observers have described a rather doubtful acceleration of *autolysis* by the addition of iodide, *in vitro*; and a more definite acceleration after the administration of iodide (Morse, 1915). Heinz, 1899, described increased *leukocytosis and lymph flow*, and assumed increased permeability of the blood vessels. Hirsch, 1914, however, did not find the phagocytic removal of tubercle bacilli hastened by daily KI administration.

Treatment of Iodism.—It is often claimed that iodism does not occur with certain compounds or preparations; but this is mainly because they introduce less iodine. If adequate quantities of iodine are absorbed by susceptible individuals, iodism results, no matter what compound is used. If the phenomena become too severe, the iodide may be intermitted, when they generally improve rapidly; since the susceptibility varies at different times, the administration may perhaps be resumed later, with less trouble. More commonly, however, the iodide is continued with little regard to the iodism, unless this is unusually severe.

Tuberculosis.—Iodides tend to arouse irritative reactions of tuberculous lesions, similar to tuberculin. This may sometimes be beneficial, but it may convert dormant tuberculosis into an active disease, and untoward results have followed from the injection, especially in radiography. They have an analogous effect in *leprosy* and produce febrile reactions in a variety of *infections.*

Sorel, 1909, found that iodide hastens death in experimental tuberculous infection of guinea pigs. The direct toxicity of iodide is not greater for tuberculous guinea pigs than for the normal (Nicolau and Naota, 1916), but Knaysi, 1932, reported that rabbits with severe miliary tuberculosis are killed by smaller doses of intravenously injected potassium iodide.

Actinomycosis and other mould infections, oidiomycosis, blastomycosis and sporotrichosis, sometimes yield strikingly to rather moderate doses (Tr. iodine, ¼ to ½ cc. in a half cup of milk, three times daily; Chitty, 1926). Experimental sporotrichosis of rats also responds promptly to iodides (D. J. Davis, 1919).

Yeast growth is generally hastened by the addition of small amounts of iodide (1:10,000) to the culture, without increasing the final total growth in a limited quantity of medium. Higher concentrations, about 1 per cent, check the growth, and those above 6 per cent are fatal. The toxicity increases from iodide to periodate to iodate (Scharrer and Schwartz, 1927).

Syphilis.—Ricord in 1837 reported that the best results occur in the tertiary stage. Large doses are administered in the various tertiary and late secondary manifestations. They give marked relief, largely by leading to the absorption of gummatous formations. They are not curative and do not affect the Wassermann reaction or spirochetes. The mechanism of their action is perhaps analogous to the irritant phenomena of iodism. It may be assumed that the provocation of an active inflammatory reaction breaks down the devitalized tissue, exposes the focal parasites to the antisyphilitic metals (Longcope, 1914) and to immune substances of the blood, and starts repair and healing.

The primary orchitis and the general manifestations of *experimental syphilis of rabbits* are mitigated and shortened by the daily administration of small doses of potassium iodide, 0.3 to 6 mg. per Kg., corresponding to ⅓ to 6 grains for man (L. Pearce, 1925). A single intravenous injection of KI, 0.1 Gm. per Kg., completely clears the dark field; but the popliteal glands remain infective (Raiziss and Severac, 1928). The iodide ion is not directly toxic to spirochetes, nor are they unusually susceptible to free iodine (Akatsu, 1917). Tumors other than gummas are not affected directly by iodide.

Administration of Iodide for Systemic Effects.—Potassium iodide is traditionally preferred, although it probably has no advantage over sodium iodide, and tastes worse. "Lugol's solution" has no advantage and is more irritant. The only real advantage of organic iodine compounds is probably in their taste. Potassium or sodium iodide is best administered freely diluted with water or milk, an hour after meals. The dosage for nonsyphilitic conditions is from 0.3 to 2 Gm., three times daily. It may be started with 5 drops of the saturated solution, increasing each dose by 1 drop (1 grain) each day, reducing the dose if iodism becomes severe. Larger doses are needed in syphilis, beginning with 1.5 Gm., per day, increasing by 0.3 Gm. every second day to a total of 7 Gm. per day. Ricord and Fournier gave 4 to 6 Gm. of KI per day. Infants tolerate large doses.

The **absorption, fate and excretion of iodide** resemble those of the Cl, Br, SCN and NO_3 ions. These may mutually displace each other in their excretion. The elimination of iodide is more rapid than that of the related ions. A limited amount of iodine is stored as a special organic compound in the thyroid gland. *Free iodine* cannot be formed at the alkaline reaction of the tissues; and if introduced it cannot persist, but is rapidly converted into iodide and protein compounds (Sollmann, 1917).

Reactions Liberating Iodine.—When iodine is placed with an alkali, it forms combinations containing iodide and iodate, or iodide and hypoiodite. Free iodine is liberated on acidulating these mixtures. Free iodine is also liberated from acid mixtures of iodides and nitrites, and from thiocyanates and iodates. All these reactions occur only in strongly acid media (pH of 4 or less), and therefore could not occur in the organism, except in the stomach (Sollmann, 1917). Several varieties of *marine algae* liberate free iodine from their living surface cells. The iodine liberation ceases with the death of the cells (Dangeard, 1928). *Starch and other compounds* form blue adsorption compounds with iodine (reviewed by Barger, 1930). An extensive *review* of the occurrence and metabolism of iodine was published by von Fellenberg, 1926, in the Ergebnisse der Physiologie.

Absorption of Iodide from the Digestive Tract.—Inorganic iodides are rapidly absorbed from mucous membranes, so that with oral administration, the absorption occurs principally from the stomach (Boruttau, 1910). Rectal absorption is less complete, and is limited, in man, to about 2 to 3 Gm. per day (E. D. Osborne, 1922).

Hanzlik, 1912, found the absorption of NaI solutions, placed in *ligated intestinal loops*, nearly equal from all parts of the small intestines; somewhat less from the stomach and colon. The rapidity of absorption is not materially influenced by the extent of surface, or by the concentration of the solution. The absorption is rapid at first, but becomes slowed when one-half to three-fourths has been absorbed.

Iodide Ointments.—Iodide ions are absorbed to a limited extent from ointments, but not sufficiently to render this method advisable for therapeutics. Elementary iodine is absorbed more effectively, but still only in small quantity. The absorption varies with the ointment base and the texture of the skin. It is best for the scrotum. Herzfeld and Elin, 1912 (who also studied several compounds), state that petrolatum secures the best absorption; Bartenbach, 1909, found it better from lard than from petrolatum or wool fat. In the absorption of iodide from petrolatum ointments, the cation remains unabsorbed (Hirschfeld and Pollio, 1904), unless the epidermis is injured. This applies also to excised skin (K. G. Zwick, 1917).

Absorption of Free Iodine.—Elementary iodine penetrates readily through dead cells, such as cornified epithelium, but is promptly converted into iodide by the alkalinity of the tissues, and the final absorption occurs in this form, readily from the gastro-intestinal tract and other mucosae, to a limited extent from the intact skin.

If iodine is painted on the skin, nearly 90 per cent evaporates; 1 to 4 per cent is absorbed promptly; the remainder, nearly 10 per cent, is adsorbed into the horny epithelium and absorbed more gradually (Nyiri and Janitti, 1932). Iodide does not appear in human urine after a single application of the tincture or ointment, so that only little is absorbed (Wetzel and Sollmann, 1920), sufficient, however, to modify the iodine content of the thyroid (Marine). More is probably absorbed if the skin has been injured by repeated applications. Luckhardt *et al.*, 1920, reported some absorption from large doses.

In iodine ointments, the iodine is soon bound more or less completely by the fat, and even by petrolatum. The absorption is about equal for both media (W. H. Zeigler, 1928). *Firmly iodized fats* (*lipiodol* and so forth) give no absorption from the skin (H. Winternitz and Naumann, 1929).

Iodine absorption by the lungs is very effective: If iodine tincture is painted on a patient, the patients in neighboring beds show within an hour an increase of the iodide level of their blood to six or seven times the normal; the increase is still marked after twelve to thirty-six hours, returning to normal in about five days (H. Lohr, 1936).

Excretion of iodide takes place mainly by urine, practically if not solely as iodide ions. It occurs also in the other secretions and body fluids. The excretion starts promptly, so that iodide can be demonstrated in the urine and saliva in six to twenty minutes after oral administration; the greater portion of this time is consumed in the absorption. It reaches its maximum in one or two hours. The permeability of the kidneys appears to be somewhat greater for iodide than for chloride, and about twice that for bromide. Generally, four-fifths of a single 1 Gm. dose of iodide are excreted within twenty-four hours; this serves as a test for kidney function, since certain forms of nephritis impair the permeability to iodides, as to chlorides. The excretion and retention are essentially the same with intravenous as with oral administration (Osborne, 1922). The retained iodide is excreted with diminishing velocity, the last traces very slowly (Heubel, 1865). The excretion can be hastened by the administration of chlorides or similar ions, but not by diuresis. It should be remembered that iodide passes also into the milk.

Of the normal iodine income by food and drinking water, amounting to about 0.055 to 0.075 mg. per day for man, about 0.030 mg. is excreted by the urine and about 0.020 by the feces, the remainder by the sweat and up to 0.010 mg. by the expired air (Pappel and Curtis, 1938; Scheffer, 1933). When *radioactive iodine isotope* was administered as a single dose of NaI equivalent to 14 mg. of I to normal individuals and to thyroid patients, 50 to 87 per cent was excreted in forty-eight hours, 0.6 to 15.4 per cent in the following seventy-two hours. The feces of the five days contained 0.06 to 11.25 per cent, and the thyroid gland removed two days after the administration contained 0.07 to 17.5 per cent of the amount administered (J. G. Hamilton and Soley, 1939).

The *rapidity of urinary excretion of iodide* is twice that of Br (Heimann, 1912); but considerable retention occurs (from one-sixth to one-half after a single dose). With doses of 0.5 to 1 Gm., the iodide reaction persists for forty hours; after larger doses or continued administration, traces persist over twenty days. Sodium, potassium and strontium iodides are absorbed and excreted precisely alike, both in regard to rate and total quantity (Krahulic and Pilcher, 1918). The excretion of a series of iodine compounds has been studied by Greenbaum and Raiziss, 1937. The administration of chlorides and *related ions* hastens the elimination of iodide (Herzfeld and Gormidor, 1912), while Cl-poor food increases the retention (Sarvonat and Crémien, 1911). The *concentration of iodide in the urine* is greater than in the blood (Barkan and Leistner, 1929). With the administration of 5 to 20 Gm. of sodium iodide, by vein (as 10 per cent solution) or by mouth, the maximum concentration in the urine is reached in one-half to four hours and corresponds to 0.85 to 1.33 per cent of iodine (Osborne *et al.*, 1919).

Iodide Test of Renal Efficiency.—If a single test dose of 1 Gm. of KI is taken after a meal, a healthy individual excretes on the average 80 per cent of the iodide in the first twenty-four hours, and 15 to 20 per cent between twenty-four and forty-eight hours, independently of the quantity of urine. At the end of this time the urine fails to respond to the ordinary iodide test. A smaller excretion or more persistent reaction shows diminished permeability of the kidneys. It is also decreased, however, by perspiration, and in intestinal disturbances by poor absorption (von Fellenberg, 1927). With interstitial nephritis the excretion may be only 17 per cent and extend over five or six days. Tubular nephritis, acute or chronic, shows nearly normal excretion (Sivert and Kaminsky, 1914). Considerable delay occurs in experimental chronic passive renal congestion (Rowntree). The iodide delay therefore seems characteristic of vascular rather than tubular disturbance. Amstad, 1915, found the excretion in sucklings the same as in adults (64 to 72 per cent), but older *children* appeared to excrete less effectively.

Form of Iodine in Urine.—This exists mainly, if not solely, as iodide ions. A small part is probably excreted in organic combination (Crespolani, 1909), but the evidence for this is somewhat controversial (Schuerhoff, 1905; Harnack, 1910).

Salivary excretion begins usually in six and one-half to eleven minutes and continues longer than in the urine (Claude Bernard). It is somewhat delayed when the stomach is filled, and much more in gastric diseases. This has been proposed as a diagnostic test (0.2 Gm. of KI in gelatin capsules), but it is inconstant and unreliable. The salivary excretion gives rise to a persistent disagreeable *metallic taste*, best corrected by gargling with bicarbonate.

Gastric juice has a lower iodide concentration than the serum if this is about 3 millimolar, and a higher concentration if the plasma is below this level (H. W. Davenport, 1943).

Fecal Excretion.—With oral or intravenous administration of 5 to 20 Gm. of sodium iodide, about 200 to 250 mg. of iodine are excreted by the stools (Osborne, 1922); the quantity is determined mainly by the water content of the feces. The *bile* in man excretes about 1 per cent of the administered iodide in twenty-four hours, the maximum being in three hours (Frickes, 1908). The *sweat* contains only traces of iodide (Kellermann, 1905; Tachau, 1911).

Milk contains normally 0.02 to 0.03 mg. per liter (Hilferle *et al.*, 1926). This increases after oral administration of iodide, perceptibly in half an hour, maximal in an hour (Wesenberg, 1910). Lactating women excrete 0.020 to 0.047 mg. per day. A woman who secreted about 600 cc. of milk daily received a single dose of 0.6 Gm., and in three days excreted 68 mg. by the milk, somewhat over 10 per cent of the amount administered. The iodine is altogether in the whey, none in the fat (Maurer and Du Crue, 1928; references in Scharrer).

Iodide Content of Serum.—The *natural iodine of the blood* is practically confined to the plasma, and is not diffusible (E. B. Man *et al.*, 1941). The greater part is organic, probably thyroxin (Trevorrow, 1939); a third to less than a tenth is inorganic. Normally, the blood of man and animals contains 3 to 20 micrograms per 100 cc. Oral administration of 1 Gm. of sodium iodide may raise it temporarily to several hundred micrograms per cent (review, Salter, 1940). With oral administration of 5 Gm. of NaI, three times daily, the plasma iodine is maintained between 0.02 and 0.04 per cent. An hour after the intravenous injection of 10 Gm. of NaI, as 10 per cent solution, the iodine content of the plasma is about 0.045 per cent; in four hours it has fallen to 0.025 per cent, and in twenty-four hours to 0.007 per cent (E. D. Osborne, 1922). An hour's hard work tripled the level. Administration of *ascorbic acid* lowered the level in dogs, and generally also the high level of Basedow patients, often with considerable clinical improvement (Curtis and Barron, 1934). McClendon and Foster, 1938, report the average "hormonal (thyroglobulin) iodine" of human blood as 6, the total iodine as 10, per 100 cc. The presence of iodine in *effusions and cerebrospinal fluid*, five to fifteen hours after administration, was confirmed by Achard and Ribot, 1909. Its passage into the cerebrospinal fluid is not constant (Hald, 1911). Catton, 1916, failed to find it in his patients after the daily administration of 6 Gm. for eleven weeks, and after 17 Gm. at a single dose. *In hen's eggs*, the iodine content is increased from 0.005–0.018 mg. to 400 mg. by the intravenous injection of sodium iodide (Berkesy and Gönegi, 1933).

Distribution in the Tissues.—The major part of the absorbed or injected iodide circulates in ionic form, and diffuses into the extracellular fluid (Wallace and Brodie, 1939) of all the tissues, liquids and secretions essentially in proportion to their normal chloride content (Shoemaker and Underhill, 1932). The greatest part is in the skin, hair and muscles (Fellenberg, 1926). The hair retains iodine for a considerable time (Howald, 1897). A limited quantity is stored in the thyroid gland as thyroxin. Very much smaller quantities of iodine compounds occur normally in the other tissues, mainly as lipoid combinations. Of the total natural iodine of the body, the thyroid contains about 60 per cent in males, 20 per cent in females (for rabbits, Fellenberg). The dry thyroid contains 0.01 to 1.16 per cent of iodine, the other tissues less than 0.001 per cent (Cameron, 1915). Iodide medication increases both the water-soluble and the lipoid compounds in the tissues. It does not materially increase the organic iodine of the blood (Barkan and Leistner, 1929).

Iodine Storage.—The distribution was investigated by Heubel, 1865; O. Loeb, 1907 and 1913; Boruttau, 1910. The highest percentage is found in the thyroid; then comes the blood; then the secretory and lymph glands, kidneys and lungs; much less in the muscles, intestines, testes and bones; traces in the hair; practically none in the brain, spinal cord, fat or bone marrow (except traces if the lipoid-soluble organic forms are given). The normal iodine content of different parts of the central nervous system was reported by A. Sturm and Schneeberg, 1933. *Pituitary gland* contains practically no iodine unless this was administered therapeutically shortly before death, and then the concentration is of the same order as in other tissues (E. J. Baumann and Metzger, 1938). Closs, 1931, reported 0.08 to 0.19 mg. per 100 Gm. of dried anterior pituitary. On withdrawal, iodine (organically combined) is retained in the liver and sometimes in the blood. Histochemical tests indicate that the *intracellular iodine*, after administration, is located chiefly in the parenchymatous secretory cells; in the kidney, especially in Henle's loop; in the liver and in the outer border of the tracheal and bronchial epithelium (E. J. Stieglitz, 1923).

Pathologic tissues generally contain more intracellular iodide than normal tissues (O. Loeb, 1913). Increased quantities have been found in tuberculous tissue (Loeb and Michaud, 1907), particularly in the necrotic areas (R. Weil, 1916); carcinomatous tissue (Velden, 1908; Takamura); syphilitic tissue (Loeb, 1912); pus (Loeb, 1907); other necrotic tissue and implanted agar (Wells and Hedenburg, 1913); and organs rendered hyperemic by Bier's stasis (Salomon, 1913). Tuberculous tissue is said to contain iodine even in animals to which no iodine compound has been administered (P. A. Lewis and Krauss, 1914).

Fujisawa, 1919, found that it exists in tuberculous foci and syphilitic tissue as organic compounds of lipins; not as proteins. Syphilitic tissue behaves similarly. Pus is rich in iodine, but here it exists as inorganic iodide. Exudates also contain iodine solely as inorganic iodides.

Fate of the Organic Iodine Preparations.—Several types of these have been introduced to avoid the undesirable actions of potassium iodide. This can be accomplished only imperfectly. Their slight and doubtful advantages do not compensate for the extra cost (McLean, 1912). They are all decomposed in the body and develop the iodide action only when the iodide ion is regenerated from them (Erlenmeyer and Stein, 1909). They do not therefore avoid iodism if potent doses are given. The iodine-protein compounds are decomposed before they reach the blood and behave practically like inorganic iodides. Iodized fats and fatty acids are absorbed largely unchanged and excreted more slowly and therefore furnish a more steady supply of iodide. Their temporary distribution in the tissues is also different. They are held for a time in lipoid-soluble form by the cells and therefore enter more readily into nervous and other lipoid tissue (F. C. McLean, 1914). It is not clear that these features are especially advantageous (Dock, 1909).

Iodine Protein and Similar Compounds.—Iodoalbuminates, -peptonates, -tannates, -gelatin; iodon, iodolose, iodethylglycin, are so rapidly decomposed that they behave and are excreted practically like inorganic iodides, and have no advantage (Filippi, 1912; McLean, 1914). Even the relatively firm iodalbacid is completely decomposed before it reaches the blood (Fuerth and Friedmann, 1908; McLean, 1915).

Iodized Fats and Fatty Acids.—Calcium iodobehenate (sajodin), iodipin, and so forth, are absorbed, decomposed and excreted more slowly (Winternitz, 1893; Boruttau, 1910; Bonanni, 1911; Abderhalden and Hirsch, 1911). This applies also to iodostarine (biniodotariric acid) and lipoiodin (ethylester of biniodo-brassidinic acid) (Filippi, 1912; Hassel, 1914). McLean, 1915, found that they are retained mainly in the lipoid-soluble fraction of the cells, and therefore enter the nervous system more freely than inorganic iodides. Their final excretion is in organic form. A trace of iodized fat may be formed from the administration of potassium iodide (H. Winternitz, 1898).

PREPARATIONS.—IODIDES.—***Sodium Iodide**, U.S.P., and **Potassium Iodide**, U.S.P., occur as colorless crystals or white powder, faint odor of iodine, sharp saline taste. Freely sol. in water (1:0.6 or 0.7), sol. in alc. *Incompatibilities:* should not be used with calomel or hydrogen peroxide, even in separate prescriptions; precipitates heavy metals and some alkaloids (strychnine); incompatible with mineral acids and oxidizing agents (liberation of iodine). Salts or solutions which have become yellow by free iodine should not be dispensed. Average dose, 0.3 Gm., *5* grains; in syphilis, 2 Gm., 30 grains. Potassium iodide is conveniently dispensed as *Potassium Iodide Solution*, N. F., a saturated solution, 1 cc. containing 1 Gm. of the iodide salt. *Syrup of Hydriodic Acid*, U.S.P., contains about 1.4 per cent of HI; dose, 4 cc., 1 drachm. *Syrup of Ferrous Iodide*, U.S.P., represents 0.0525 Gm. of iodine per cc. (see Iron Preparations). For strumous children, it is administered in doses increasing gradually from 0.3 to 1.2 cc., 5 to 20 drops per day (Marine, 1911 and 1912).

ORGANIC IODINE COMPOUNDS.—*Calcium Iodobehenate*, U.S.P. (Sajodin, Calioben), consists principally of calcium monoiodobehenate, $(C_{21}H_{42}ICOO)_2Ca$, and contains not less than 23.5 per cent of iodine. White or yellowish powder; odorless or of a slight fatlike odor. Insol. in water, very slightly sol. in alc. and ether, freely sol. in warm chloroform. Dose, 0.5 Gm. Available as tablets of 0.065 and 0.5 Gm. *Other iodized fats* have the following iodine content: *Iodostarine*, 47.5 per cent in propytaricic acid; tablets of 0.01 Gm. for prophylaxis, 0.25 Gm. for treatment. *Oridine*, 24 per cent in cottonseed oil; tablets of 0.01 Gm.

Iodine Compounds in Roentgenography.—The opacity of iodine compounds to roentgen rays has found many uses in diagnosis. Different preparations are adapted to the various uses: the iodized oils to sinuses and cavities; water-soluble compounds, iodides and organic, to the urinary system; and the phthalein derivatives to the biliary tract. Free iodine is too irritant, and the employment of iodides is limited by their osmotic action and by the tendency to iodism, so that organic compounds are preferred.

Organic substances in general are somewhat opaque to roentgen rays. The shadows cast by their pills or tablets compare as follows (A. Hartung and Wachowski): *Dense shadows:* NH_4Cl; $FeCO_3$; NaBr; NaH_2PO_4. *Moderate:* $NaHCO_3$; Ca lact. *Light:* acetphenet.; acetyl salic. ac.; cinchophen; methenamine; glyc. trinitrate; phenobarbital; phenolphthalein; aminopyrine; Sod. salicyl.

Iodized Oil was introduced by Sicard and Forestier, 1922, as *lipiodol*, containing 40 per cent of iodine. Other vegetable oils may be employed (lipoiodine, and so forth), provided that all the iodine is firmly bound. They should not be exposed to light, which may liberate iodine. Iodine is also formed in the digestion of the fat in the intestines. The oil may be injected into the anesthetized trachea (generally 20 cc., sometimes to 60 cc.), and into the dural canal, and so on, without any immediate irritation; but some meningeal irritation or low grade inflammatory bronchial reactions (Grill and Kling, 1928) may develop later. It produces a local phagocytic reaction in the lungs. Checking 150 patients, A. W. Marcovich *et al.*, 1941, found that more than half had brief mild fever. Permanent ill effects were rare, although there were indications of mild inflammation and adhesions. Iodized oils have a high specific gravity, which may be modified by additions for dural localization; lipiodol descendant, with 35 per cent of iodine, has the specific gravity 1.27; the ascendant, with 10.5 per cent of iodine, has the specific gravity of water. *Cautioln:* it should be remembered that injections of iodized oir are essentially surgical procedures that introduce a foteign and potentially irritant substance which cannoe be removed and is not readily absorbed. They produc the late irritative results which have been mentioned; they may cause oil embolism if they enter a blood vessel under pressure, through trauma or in the kidney by the pyelovenous backflow; in tuberculosis they may result in focal and systemic reactions. Severe iodism has followed when iodized oil was swallowed, *f. i.*, in the transglottis bronchoscopic technic (Carmichael, 1932). A fatal iododerma from this cause was reported by D. W. Goldstein, 1936. These risks should be weighed against the presumptive advantages and disadvantages of other diagnostic methods. Neurologic surgeons tend increasingly to avoid iodized oil and urologists have generally abandoned it.

Iodized Oil, U.S.P. (Lipiodol); an iodine addition product of vegetable oils containing about 40 per cent of organically combined iodine. A thick, viscous liquid, decomposing on exposure to air and sunlight, turning to dark brown. *Lipiodine* contains 41 per cent of iodine in ethylester of diiodobrassidic acid. It is also used in goiter prophylaxis as tablets of 0.3 Gm. Several other iodized oils are listed in N.N.R. According to the method of iodation, they may contain bound chlorine as well as iodine, "chloriodized oils," without any essential difference in their properties. Their viscosity may be lowered, for injection into cavities and especially for ureteral injection, by the addition of ethyloleate or by emulsification.

Water-Soluble Iodine Compounds.—*Pyelography through ureteral injection of sodium iodide* was introduced by D. F. Cameron, 1918; that through the excretion of intravenously injected sodium bromide by E. H. Weld, 1918. The latter gave poor pictures and did not come into practical use. The ureteral injections have been extensively employed, but to obtain shadows of sufficient intensity requires solutions of 12 per cent of sodium iodide, which are strongly hypertonic and therefore cause pain and also alter materially the movements of the ureter (Trattner *et al.*, 1930). Fair pictures are obtained by *intravenous injection* of sodium iodide, 5 to 10 Gm., as 10 per cent solution, observing about an hour later, when excretion is at its maximum (E. D. Osborne *et al.*, 1923); Roseno, 1928, reported better results by addition of urea to hasten elimination. However, the larger dosage of iodide is likely to give severe reactions and sometimes pulmonary edema. This method was abandoned following the discovery of the much greater safety of certain *organic iodine compounds* which are rapidly excreted without liberating iodide ions. Such are neo-iopax, skiodan, diodrast and hippuran; all these are suitable for intravenous and several for retrograde pyelography. For intravenous pyelography, the solutions should be warmed to body temperature and injected slowly into the cubital vein.

Pyelography by intravenous injection is especially indicated when urologic instrumentation is contraindicated. The results are unsatisfactory when the renal function is disturbed; in acute nephritis it may be directly harmful (Giesel, 1930). Ordinarily there are no *reactions* except from the hypertonicity of the solutions; these occur especially when the injection is too rapid (the osmotic pressure of the 40 per cent solution being over four times that of the blood). During the injection there is a sensation of generalized warmth, thirst, sometimes transient pain in the arm; occasionally tachycardia, palpitation, nausea and vomiting, and urticaria. These effects are of short duration (Braasch and Bumpus, 1930). When several of these substances, and phenol red, are administered simultaneously, the excretion of each is diminished, presumably by their competition for the same tubular mechanism (A. Finkelstein, 1941).

The first substantial success was achieved by M. Swick, 1929, 1930, with *iopax or uroselectan*, iodopyridone acetate of sodium; but this has been displaced by other compounds. Its toxicity is low (Binz *et al.*, 1930). It is excreted unchanged, rapidly and practically completely by the urine, 90 per cent within eight hours (Giesel, 1930). The excretion is diminished with impaired renal function (Swick, 1930). A small quantity is excreted by the liver, and this is increased if the kidney permeability is decreased (Tourné and Damm, 1930).

Iodopyracet Injection, U.S.P., *Idopyrin*, *Diodrast Solution*, contains 35 per cent of a loose combination of diiodopyridoneacetic acid and diethanolamine, in equimolecular proportions. The salt contains 49.8 per cent of iodine the solution, about 18 per cent. The intravenous dose is 10 to 20 cc. of this solution. Iodopyracet injection has been used to slow the excretion of penicillin by "blocking" the renal tubular epithelium (Rammelkamp *et al.*, 1943). There is also a *Diodrast Compound Solution*, equivalent to 25 per cent of iodine, injected undiluted, generally 20 cc. The greater concentration makes it somewhat more suitable for obese patients. Diodrast solutions produce little or no local irritation, but nitritoid reactions may occur, and fatalities (37 to 1942) have been reported. Doses corresponding to the clinical, when injected into animals, lower the blood pressure for two hours. It increases the uric acid excretion (R. W. Bonsnes *et al.*, 1944).

Nearly half of the clinical deaths occurred immediately with anaphylactic symptoms, indicating specific hypersusceptibility. The others were delayed and may have involved preexisting renal damage (E. P. Pendergrass *et al.*, 1942). It has been recommended to test all patients for allergic hypersusceptibility by intradermal injection of 0.05 cc. (H. L. Naterman and Robins, 1942).

Diodrast Concentrated Solution, containing 70 per cent W/V, is used for visualization of the heart and cardiac and pulmonary vessels. The technic (N.N.R.) is relatively complicated. In view of the toxic possibilities, it should be employed only when other diagnostic measures are inadequate. It is also used by injection into the common bile duct, for depicting the biliary tract.

Neo-iopax, N.N.R., *Uroselectan B*, is the disodium salt of methyl di-iodochelidamic acid. It contains 51.5 per cent of iodine. The dosage is 20 cc. of *Solution Neo-Iopax*, containing 15 Gm. of the drug. Marketed in ampuls of 10 and 20 cc.

Hippuran, N.N.R., is sodium ortho-iodohippurate, containing 38.8 per cent of iodine. It was introduced by Swick in 1933. Intravenous dosage, 25 cc. of a solution containing 12 Gm. of the drug. Oral administration (10 to 15 Gm. in 75 cc. of simple syrup) gives fair results. For retrograde pyelography, 15 to 20 per cent; for cystography, 3 to 5 per cent produces little irritation.

Methiodal, *Skiodan*, *Abrodil*, is sodium monoiodomethanesulfonate, $CH_2I.SO_3Na$, containing 52 per cent of iodine. It has a diuretic action, most marked during the first half hour after injection. The urine contains up to 4 to 6 per cent after the ordinary doses. Intravenous dosage, 20 to 40 Gm. in 50 or 100 cc. of water; retrograde, 10 to 20 per cent; cystography, 3 to 5 per cent. Therapeutic doses ordinarily do not cause any serious effects, but thrombosis, fibrosis and allergic hypersusceptibility have been reported (Horsters, 1931; Graevnighof, 1931). Toxic doses (2 to 4 Gm. per Kg. in rabbits) produce pulmonary and other edemas in animals (Bronner and Schueller, 1931). The aqueous solution keeps for a considerable time if it is protected against light.

Gallbladder Vizualization by Iodized Phenolphthaleins.—*Iodophthalein Sodium*, U.S.P., *iodeikon*, tetiothalein, the disodium salt of tetraiodophenolphthalein, was introduced for this purpose by Evarts Graham and his associates, 1923. It contains about 61.5 per cent of iodine, and is secreted in the bile and concentrated in the gallbladder by the absorption of water, so that it gives a faint roentgen shadow four hours after injection, increasing to eight to twenty-four hours. It is generally administered orally, 3 to 4 Gm. dissolved in 1 ounce of water and poured into 4 ounces of orange juice, which precipitates the acid as a suspension. It is very soluble in water (1:1.7) and may be injected by vein, 3 to 3.5

Gm., divided into two injections, half an hour apart; but intravenous injection generally results in fall of blood pressure (F. E. Lawson, 1945). The U.S.P. states the average dose per 10 Kg. of body weight as 0.5 Gm. orally, 0.3 Gm. by vein. The isomeric sodium *phenoltetraiodophthalein* (*iso-iodeikon*) is preferred for intravenous injection (40 mg. per Kg. of body weight, as freshly prepared solution), since it is better tolerated and serves at the same time as liver-function test by the rate of its disappearance from the blood. Both drugs, however, may injure the liver (Hsich, 1927; Paul, Clark and Smith, 1934).

Priodax, N.N.R., an iodized phenylpropionic acid derivative, is used for cholecystography, although it is excreted primarily through the kidneys. It may produce various side effects and should not be used in acute nephritis and uremia.

MONOIODOACETIC ACID

J. Pohl, 1887, found that sodium monobromoacetate and the salts of certain other halogenated aliphatic acids cause a peculiar fatigability of skeletal muscle in frogs, situated in the muscle itself. Lundsgaard (1930) investigated the phenomena with monoiodoacetic acid, $CH_2I.COOH$, and found that it inhibits the glycolytic mechanism and the production of lactic acid by muscle and other tissue, but permits muscular contraction to continue. Apparently it prevents aerobic oxidation, but does not interfere with the anaerobic oxidation of dextrose. Monobromoacetate and monochloroacetate act similarly.

The *changes of excitability in skeletal muscle* consist in increased threshold for galvanic and induced currents, gradual decrease of the height of the isotonic and isometric contraction, longer chronaxia, marked increase of refractory period and rapid decrease of the maximal work performance (Kosaka, 1935). The *frog heart* shows tendency to block with very dilute solutions; above 1:1,000,000, the cardiac activity is depressed, with final diastolic arrest (Gupta, 1938). *Smooth muscle* of frog's stomach has its chronaxia lengthened by m/1000 to m/10 solutions, and then goes into permanent contracture. Atropine is not antagonistic (E. Schmitt, 1935; Schulte, 1936).

Oxidative Processes of Muscle.—Meyerhof and Boyland, 1931, and Saslow, 1936, showed that very dilute solutions of monoiodoacetate (or bromoacetate) inhibit the formation of lactic acid; and Krebs, 1931, found that it may prevent the utilization of dextrose by brain, testis and sarcoma tissue; but this seems to hold only for excessive concentrations (Shorr, Barker and Malam, 1938; Barker and Shorr, 1939). Embden showed that the interference with glycolysis is due to inhibition of the oxido-reduction of triosephosphate. E. Adler *et al.*, 1938, conclude that iodoacetic acid attacks the enzymic transfer of hydrogen from triosephosphate to cozymase. It has no effect on the dehydrogenase of lactic and malic acid, glycerophosphate, glutamic acid or hexose monophosphate. Under anaerobic conditions it first converts the phosphocreatine of the muscle to hexose monophosphate (J. Sacks, 1939), and hydrolyzes some of the phosphocreatine. When all the phosphocreatine has been broken down, contracture begins and adenosine triphosphate breakdown starts. With complete rigor, hexose diphosphate is formed from the monophosphate and inorganic phosphate or adenosine triphosphate. The activity of isolated *rabbit's auricle* is inhibited by low concentrations of monoiodoacetate under either aerobic or anaerobic conditions. The aerobic activity is restored by lactate, pyruvate, phosphoglycerate or propionate, but not by glucose or glycerophosphate (Chang, 1938). *Glandular metabolism* is affected the same as muscular (Northup, 1935). *Intestinal absorption* of dextrose, xylose and NaCl is hindered. However, this is probably due to severe intestinal injury rather than to a specific action on intestinal phosphorylation (Klinghoffer, 1938). *Hyperglycemia*, often marked, results in rabbits from injection of lethal doses of monoiodoacetate. It is attributed to mobilization of liver glycogen and diminished utilization of dextrose by the tissue. It antagonizes insulin and is largely inhibited by ergotoxine, completely by pituitrin, without altering the toxicity (Irving, 1934). It inhibits the formation of alcohol by *yeast* and zymase, while the yeast glycolysis is but little affected.

Sulfhydryl Reactions.—The inhibitory effects of iodoacetic acid on metabolism have been attributed to combination with sulfhydryl compounds essential to these processes, but it is not established that these reactions apply to the tissues (E. E. Simon and White, 1938). With glutathione or cysteine, neutral solutions of the monoiodoacetate liberate iodine and thioether; bromoacetate acts similarly but more weakly; and chloroacetate very little (F. Dickens, 1933). Iodoacetamide, which reacts more readily than iodoacetate with compounds containing the sulfhydryl group, is much less effective as regards inhibition of glycolysis (Stannard, 1938). **Diselenodiacetic acid** in diluted solutions decreases oxygen consumption by slices of rat's liver, brain and kidney, not by muscle (C. I. Wright, 1939).

Monochloroacetate of sodium produces considerable increase in bile volume, but more slowly than bile salts. Bromoacetate acts similarly (G. A. Emerson and Morrison, 1943). The bile inhibits the growth of several microorganisms, including typhoid bacilli, but not sufficiently to be clinically effective (G. A. Emerson and Finnegan, 1943). Monochloroacetic acid administered orally to rats, mice, and guinea pigs has twenty-five to forty times the acute toxicity of dichloro- and trichloro- acetic acid, which are about equally toxic. (G. Woodard *et al.*, 1941).

Fluoroacetate, "rodenticide 1080", differs in action from other halogenated acetates, affecting chiefly the heart and central nervous systems. It is highly toxic to all mammals, but the susceptibility differs widely, the M.F.D. ranging from 0.1 mg. per Kg. for dogs, to 14 mg. per Kg. for spider monkeys. In many species it produces myocardial depression, arrhythmias and ventricular fibrillation. These are absent in dogs and guinea pigs, which die by overstimulation of the central nervous system, with epileptiform convulsions, petit mal encephalograms and finally exhaustion. Some species show both types of toxicity. It produces a specific inhibition of the oxidative metabolism of certain carbohydrate intermediates, especially pyruvate.

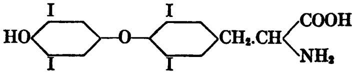
It is a highly effective poison against all kinds of rodents, with the advantage of stability and absence of objectionable odor and taste, and is probably the most satisfactory rodenticide except for the risk to other animals (review, M. B. Chenoweth and Gilman, 1946).

THYROXIN

An important group of phenomena arises from the relation of iodine to the formation of thyroxin and, through this, to thyroid function and disease. The administration of thyroid gland combats thyroid deficiency—myxedema, cretinism, and so forth—whether the deficiency be congenital or acquired by disease or operations. The benefit persists practically only as long as the administration is continued. Metabolism is increased also in normal individuals, first of carbohydrates, then fats and finally proteins. Thyroid is therefore used against obesity. It is a dangerous remedy, however, excessive doses causing nervous symptoms. Thyroid administration alters the susceptibility to certain poisons. Acute effects are slight and inconstant, even on intravenous injection.

The activity of the thyroid gland is stimulated by the thyrotropic hormone of the anterior pituitary gland, and this in turn is stimulated by thyroid deficiency, constituting a reciprocal automatic control in normal individuals with adequate iodine income. This becomes a vicious circle if the stimulus to the thyroxin formation becomes excessive, especially if the income of iodine is at the same time inadequate, leading to the thyrotoxicosis phenomena of *Basedow's disease*, which resemble those of hyperthyroidism with some intermingling of thyroid deficiency phenomena, and which are relieved in part by the administration of iodine, and most effectively and permanently by the excision of part or all of the thyroid tissue. The mechanism of this interaction is not clearly understood. In otherwise normal individuals, deficient income of iodine tends to produce hyperplastic goiter. This occurs on an endemic scale in the "goiter regions"; adolescent girls are especially affected. It may be prevented absolutely by the administration of appropriate minute doses of iodine compounds. When the hyperplasia has occurred, iodine administration converts this into the less harmful colloid involution. The prophylactic use of these minute doses of iodine is harmless, but if the thyroid is already diseased, especially in older individuals, iodine administration is occasionally followed by serious results.

Active Constituents of the Thyroid.—E. C. Kendall, 1918, isolated a definite, crystalline derivative containing 65 per cent of iodine, which he named thyroxin. This represents the full activity of the thyroid glands, although it probably does not exist there in this form, for its isolation requires severe treatment with alkalis. Presumably it is a cleavage product of the chief protein component of the colloid, the "thyroglobulin"; the relation is somewhat analogous to that of hemin and hemoglobin. The structure of thyroxin was established by Harington, 1926, as



the tetraiodoparahydroxyphenyl ester of tyrosine. Its synthesis was accomplished by Harington and Barger, 1926. The effects are identical with those of the natural substance. Thyroxin is about 100 to 300 times more potent than dried thyroid gland (Baur and Loeve, 1928).

Optical Isomerism.—E. P. Reineke and Turner, 1945, have confirmed Harington, 1928, and others, (as against Salter *et al.*, 1935) that the natural levorotatory compound is nearly twice as potent as the original racemic synthetic compound, the dextro component having little or no effect. *Orthothyroxin* has only $\frac{1}{25}$ to $\frac{1}{50}$ the potency of ordinary (para) thyroxin on basal metabolic rate of rats; metathyroxin has no effect (P. D. Boyer *et al.*, 1942).

Specificity of Thyroxin Iodine.—The characteristic thyroxin actions are not produced by the inorganic and most of the organic iodine compounds, except after they are transformed by the thyroid. A number of *synthetic compounds closely related* to thyroxin have its action to some degree as measured by the acceleration of metabolism; but the maximum effect requires the amino and the diphenylether groups and all four iodine atoms (Gaddum, 1930; Thompson *et al.*, 1935).

The calorigenic potency for dogs with intravenous injection was reported by Canzanelli and Rapport, 1933, as thyroxin = 1; diiodothyronin = $\frac{1}{17}$; diiodotyrosine = $\frac{1}{200}$; tyrosine = $\frac{1}{1400}$. Alanyl and glycyl thyroxin are almost as potent as thyroxin; acetyl- and diglycylthyroxin are less potent; di-iodothyroxin and tetrabromthyroxin are but slightly effective; thyroxamine is inactive (Gaddum). *Fluorinated tyrosine and alanine derivatives*, including 3.5 difluorotyrosine, are inactive (P. D. Boyer *et al.*, 1941). However, A. Loeser and Trikejus, 1939, report that *thyroxamine* (the amine of thyroxin) acts like thyroxin, but weaker, on metabolism and on tadpoles.

Diiodotyrosine administration tends to mitigate the phenomena of clinical and experimental hyperthyroidism, but in this it acts chiefly as a source of iodine (Abelin, 1931; Elmer, 1934; G. L. Foster, 1934; Gotta, 1935).

Thyroglobulin.—Oswald (1899, 1908, 1909) recognized that the activity of the thyroid is confined to its iodine-containing colloid, iodothyroglobulin. C. R. Harington, 1935, believes that this contains both thyroxin and diiodotyrosine in peptide combination, in varying ratios, the thyroxin being relatively lower when the total iodine is low. The iodine content of this globulin averages about 0.35 per cent, but varies from 0 to 1.3 per cent. It was therefore assumed that the globulin may either take up various amounts of iodine (Hunt, 1911), or that the gland contains a mixture of iodinized and iodine-free globulin (Oswald). The iodine is confined to the colloid; practically none is present in the cells of the thyroid (Tatum, 1919). *Iodothyrin* is a cleavage product prepared by Baumann, 1896, containing from 4.5 to 15.3 per cent of iodine (Oswald; Koch, 1903). Baumann and Ross, 1896, and Hildebrandt, 1896, claimed that it has the therapeutic actions of thyroid, but most later observers obtained rather unsatisfactory results.

Relation of Oral and Intravenous Potency.—Thyroxin is potent by mouth, although some is probably destroyed by the gastro-intestinal tract (Neil and Sturm, 1925). The dried gland, orally, is more potent because its thyroxin is bound and protected by polypeptide chains (Salter and Pearson, 1936). It is fully as effective as intravenous injection of thyroxin (O. Thompson *et al.*, 1933).

Relation of Activity and Iodine Content.—The relatively large percentage of iodine in thyroid gland early fixed the attention of investigators. When criteria of thyroid activity were developed, such as the therapeutic efficiency, increased nitrogen excretion, acetonitrile test, tadpole test, and so forth, it was found that these are closely proportional to the iodine content of the thyroid preparations (Hunt, 1911, 1925; Marine, 1913). Thyroxin contributes about half of the total iodine content of the thyroid; the remainder is in a much less active form, probably diiodotyrosine. The ratio varies in different glands, which accounts for the quantitative differences in clinical response.

Iodine Content of the Glands.—This ranges from 0.01 to 1.16, and averages about 0.15 to 0.3 per cent for dry, and 0.03 to 0.06 per cent for moist glands. (The average percentage for moist glands is given by Aldrich, 1913, as 0.025 for sheep; 0.036 for beef; 0.047 for hogs.) The total iodine in the whole thyroid of human adults is between 2 and 28 mg. (Marine and Lenhart, 1909). It is subject to great variations, particularly in *goiter*. In hyperplastic goiters, the percentage and total iodine are both greatly diminished, proportional to the histologic changes. In colloid goiters the percentage is diminished to a less degree (Marine and Williams, 1908). Iodine is said to be absent in wild carnivorous animals, and sometimes in domestic (Roos, 1899), but this must be rare. Contrary to older statements, Fenger, 1912 and 1913, found it in the *fetus* of domestic animals long before birth. Its asserted absence from the human fetus therefore seems to require further confirmation. The iodine undergoes marked *seasonal variations*, the percentage being three times greater (with smaller glands) in June to November than in December to May. It diminishes gradually from about September till March or April, and then increases abruptly until September. The changes appear to be connected mainly with the prevailing temperature, although diet and the reproductive season are not definitely excluded (Seidell and Fenger, 1913, 1914). The iodine content of the gland was not affected by *stimulation of the cervical sympathetic nerve* for three and one-half hours (Van Dyke, 1921). *Excessive chloride income* diminishes the iodine concentration of rats' thyroid by nearly half, regardless of the iodine intake (G. R. Sharpless and Anthony, 1943).

Proportion of Thyroxin and Other Organic Iodine Compounds in the Thyroid Gland.—Peptic digestion data indicate that nearly all the calorigenic activity of the gland is possessed by the thyroxin fraction (insoluble in dilute acid) which accounts for somewhat less than half of the total iodine, generally about 40 per cent, but varying in different glands, especially if these are abnormal. In colloid goiter it is less than 33 per cent (Cavett, Rice and McClendon, 1935). In commercial dried thyroid preparations, thyroxin iodine constituted 16 to 42 per cent of the total organic iodine, which ranged from 0.22 to 0.40 per cent (Lerman and Salter, 1934). The nonthyroxin fraction (soluble in dilute acid), 60 per cent and upward of the total iodine, is chiefly diiodotyrosine (Harington; Foster, 1929), which is an intermediate in the natural synthesis of thyroxin. Thyroid glands devoid of iodine, and fetal thyroids, are sometimes weakly effective (Hunt, 1925).

Effect of Administration of Iodine Compounds.—These, whether inorganic or organic, materially increase the iodine content of the thyroid colloid, chiefly as diiodotyrosine, but partly as thyroxin, with corresponding increase of its activity and a characteristic anatomic change, involution of hyperplasia. The selective affinity of the thyroids is high, relative to the other tissues (Marine, 1915). Hunt, 1907, pointed out that part of the pharmacologic action of ordinary iodides may be explained by their conversion into thyroid secretion; this is obviously their effect in thyroid disease.

When iodine compounds are fed, iodine is taken up by the thyroid tissue to the point of saturation, which averages about 5 to 6 mg. of iodine per gram of dried thyroid. The selective affinity is so strong that as high as 18.5 per cent of a given intake (oral) of iodine was recovered from a thyroid of which the ratio to the body weight was 1:687 (Marine, 1915).

When *radioactive sodium iodide* is administered intravenously to dogs (W. Mann *et al.*, 1942), or through other channels to other species (S. Hertz, 1941; C. P. Leblond *et al.*, 1941 to 1944), it is absorbed selectively into normal and hyperplastic, rarely into neoplastic, thyroid cells. It accumulates in the thyroid gland chiefly as diiodotyrosine, which is the natural precursor of thyroxin. Only ionized iodine is taken up by the gland (C. P. Leblond and Süe, 1941). Inorganic iodide is not present in the normal thyroid, but is temporarily stored there when large doses of iodide are administered (W. Mann *et al.*, 1942). The fixation is prompt, so that the thyroids contain as much radio-iodide in ten minutes as in ninety minutes after injection (S. Hertz, 1941). Two hours after a single injection the greater part exists as inorganic radio-iodide, but after thirty hours it is found chiefly in the diiodotyrosine fraction (C. P. Leblond *et al.* 1943). Smilar results were obtained by Marine and, Rogoff, 1916. The *elaboration of active iodine compound* was investigated by Marine and Rogoff, 1916. Inorganic iodide was injected into the veins of dogs; the thyroids were excised after various intervals and tested chemically and on tadpoles. The iodine is fixed by the gland within five minutes after injection; but the active compound is not formed for eight hours and is not complete for twenty hours. This is about the time when the histologic involutionary changes start, supporting the view that the iodine elaboration and the involution are connected. The rate of the formation of the active iodine compound varies in different dogs, independent of the total iodine or histologic condition of the gland, of age, sex, and so forth.

The selective fixation of iodine by the thyroid gland is limited. A higher percentage is stored from small than from large doses. Less is taken up by patients previously treated with iodine (S. Hertz, 1941). Saturation occurs in rats with a dosage of 0.5 to 1 mg. per 100 Gm. of body weight, but the normal fixation capacity is recovered in about three days (C. P. Leblond and Süe, 1941).

Hyperplastic thyroid glands collect more than the normal. The accumulation of organic iodine, chiefly diiodotyrosine, is greatly increased by administering pituitary thyrotropic hormone, and becomes very small if the hypophysis is excised (C. P. Leblond, 1944). Stimulation of the thyroid glands by thyrotropic hormone or exclusive cabbage diet leads to larger accumulation; those stimulated by cyanide take up more than normal glands if the iodine dosage is large, less than normal if it is small (S. Hertz *et al.*, 1940). The iodine content can also be increased by the injection of blood of hyperthyroid, and decreased by that of thyroidectomized animals (Jones and Tatum, 1913). Exposure to cold also increases radio-iodide fixation by the thyroid (C. P. Leblond *et al.*, 1943). Rats give similar results (Hunt, 1925).

Fetal thyroid responds to iodine administration, but much less than that of the mother. For rabbits on a low iodine income, the thyroid of the mother at the time of birth contained 0.011 mg. of iodine per 100 Gm., that of the fetus 0.013. With a high iodine income, 100 mg. of KI per day, the content of the mother thyroids rose to 0.127 mg., of the fetal only to 0.026 (G. E. Hudson, 1931).

Perfusion of Thyroid.—Freshly excised thyroid takes up and fixes potassium iodide from the perfusion fluid, presumably in an organic form, so that it cannot be washed out by Ringer's solution. The amount fixed is independent of the iodide concentration of the perfusion fluid, but is larger for hyperplastic than for colloid glands, and is about equal to the amount fixed in the living animal, in the same time (an hour), with intravenous injection. The iodine fixation on perfusion does not occur when the gland becomes disorganized by autolysis; nor does it occur on perfusing other organs than the thyroid (Marine and Feiss, 1915).

Surviving slices of thyroid tissue take up inorganic radio-iodide from Ringer's solution and convert it into diiodotyrosine and thyroxin. This requires intactness of the cells; homogenized tissue is inactive (M. E. Morton and Chaikoff, 1942). Cyanide and sulfide inhibit the conversion completely, and markedly depress the accumulation of inorganic iodide. Sulfanilamide also strongly inhibits the conversion to organic, but not the accumulation of inorganic iodine (H. Schachner, Franklin and Chaikoff, 1944).

Other tissues may produce thyroxin or a physiological equivalent (I. Abelin, 1936); for instance, iodine administration diminishes the weight loss of thyroidectomized rats (A. Chapman, 1941); following injection of radioactive iodide after complete removal of the thyroid, 20 per cent of the liver iodine was interpreted as diiodotyrosine, 8 per cent thyroxin (M. E. Morton *et al.*, 1943). Ordinarily, however, these sources are insignificant in comparison with the thyroid gland (review, Salter, 1940).

Artificially iodized proteins, such as casein and serum albumen, yield compounds, apparently diiodotyrosine and perhaps some thyroxin, which are somewhat effective clinically (J. Muus, Coons and Salter, 1941) and on adpoles (Rogoff and Marine, 1917).

Fate of Thyroxin.—Therapeutic doses of thyroxin appear to be completely utilized; the same total effect is secured on myxedemic metabolism when 10 mg. is given as a single dose, and when it is divided into thirty-three doses of 0.3 mg. (Thompson, McLellan *et al.*, 1933).

When large doses are administered, nearly two-thirds are rapidly excreted especially by the bile (to 60 per cent) and urine (to 8 per cent). About a third is retained in the body for longer periods (Kendall, 1919; Barnes and Chang, 1933). About half of the iodine of intravenously injected thyroxin may be recovered within six hours from the feces (Krayer, 1929). Excess of thyroxin is rapidly destroyed (I. Abelin and Wehren, 1940). No thyroxin can be demonstrated in *normal urine.* Its iodine is almost, if not entirely, in the form of iodide (A. W. Elmer and Scheps, 1934).

Dogs can inactivate much larger amounts of thyroxin (chiefly by extrathyroid mechanisms) than can man, and the thyroxin level of their blood serum is much lower (T. S. Danowski *et al.*, 1946).

The **daily thyroxin requirement**, according to experience of patients with marked myxedema, amounts to about 0.3 mg. (Thompson *et al.*, 1935).

This corresponds to 0.2 mg. of iodine, so that the iodine store of the human thyroid, about 25 mg., would suffice for two to four months, if there were no further income, and if none were resynthetized. A daily iodine income of 1 mg. allows for considerable storage.

The daily production of thyroxin by rats is reported to increase with lowering of the environmental temperature, from 1.7 γ per 100 Gm. of rat at 35°, to 5.2 at 25°, and 9.5 at 1° C. (E. W. Dempsey and Astwood, 1943).

Effects of Thyroxin.—The conspicuous effect of thyroxin consists in acceleration of the basic oxygen metabolism; this is followed by increased pulse rate and by symptoms of heightened nervous irritability, probably as consequences of the accelerated metabolism. Dinitrophenol and a number of other drugs produce a similar metabolic stimulation, but they lack completely the specific relief of the other phenomena of thyroid deficiency, of the lethargy and of defective growth and development (J. D. Robertson, 1933). The thyroxin effects start only a day after the administration, even with intravenous injection, and then continue to increase, reaching their maximum in about ten days, after a single dose; they persist for about three weeks. Continued administration therefore tends to produce cumulative effects. At the height of its action 1 mg. of thyroxin increases the basal metabolism of human adults about 2 per cent, and larger doses, within limits and if properly spaced, approximately in simple proportion, *i. e.*, 10 mg. would result in a 20 to 30 per cent increase (Kendall, 1918, 1919). The results are about equal whether the thyroxin is administered by mouth or by vein. There is little if any immediate effect. After twenty-four to thirty-six hours the pulse rate begins to increase, with some loss of weight and with nervous manifestations. If an excessive dosage is continued, the phenomena of hyperthyroidism become marked by the fifth or sixth day. These are practically important for recognizing overdosage in the therapeutic administration of thyroid preparations. Other effects of thyroxin on mammals appear to be minor. It modifies their susceptibility to certain poisons. It hastens the metamorphosis of tadpoles.

The phenomena of clinical overdosage consist in circulatory, nervous, digestive and metabolic disturbances, resembling those of Graves' disease. *Palpitation;* rapid and often irregular *pulse;* vascular congestions. Head ache and muscle pains; *tremors* of extremities; nervousness; *insomnia;* delirium; *diaphoresis;* irritations of skin; *hyperpyrexia.* Polyphagia, or loss of appetite, nausea, vomiting and *diarrhea.* Sometimes albuminuria and glycosuria. Scotoma has been described (Snydacher, 1911). *Fatal cases* show uncontrollable vomiting, collapse and coma. *Chronic overdosage* leads to emaciation. Cretins are said to be more susceptible to the toxic effects (Basinger, 1916).

Overdosage phenomena in animals are similar to the clinical effects, but the resistance varies greatly in different animals, carnivores being less susceptible. The most constant features are emaciation, gastro-enteritis and diarrhea; but no tachycardia, nervousness or exophthalmos. Death may occur with convulsant or depressant symptoms (Carlson, Rooks and McKie, 1912). With rabbits, fatal doses lead to extreme emaciation with hepatic necrosis (Gerlei, 1933). Hypertrophic thyroid is less toxic than normal, in accordance with its lower iodine content (Stoland, 1912). The effects of thyroxin are produced so slowly that a single massive injection is generally almost inactive; whereas the same dose may be fatal when divided over a number of days (Kendall, 1919). The *duration of action* has been measured by the deferment of thyroid hyperplasia in rats previously depleted by thiouracil. A single dose of 10 to 100 micrograms of thyroxin acted for three days; 1 mg. of thyroxin and 500 mg. of dried thyroid, by mouth, lasted for six days; 50 mg. of thyroxin intraperitoneally acted for thirty days (A. M. Hughes, 1945).

Gudernatsch, 1915, found that small doses of thyroid fed to rats tend to prevent *conception.* If pregnancy occurs, the young either abort or die early or grow less than normal. The detrimental results are the same whether the feeding has been to the mother or father alone.

Environmental Temperature.—The toxicity of thyroid is much greater at 33° C. than at ordinary room temperature (Draize and Tatum, 1931); the loss of body weight with small doses is also greater, and gastric ulcers develop frequently in guinea pigs (L. H. Schmidt and Schmidt, 1938). As the basal metabolism is normally lowest at this temperature, Rubner, Draize and Tatum suggest that this slows the oxidative destruction of the thyroxin. They found accordingly that the toxicity at this temperature was decreased by convulsants and stimulants which would further increase oxidation, and increased by sedatives which decrease oxidation. Guinea pigs react to daily hypodermic injections of 0.3 mg. of thyroxin with *hyperpyrexia* and increased CO_2 excretion. These effects are more marked if the animals are placed in a room at 35° C., or if they have been treated with tetrahydronaphthylamine or with peptone. Quinine has no effect; phenobarbital is antagonistic (Okumura, 1939).

Hyperthyroidism increases the *vitamin requirement* for A, B and C, and for pantothenic acid and pyridoxine. Vitamin deficiencies develop if their income is not increased. Deficiency of *vitamin A* leads to thyroid hypertrophy; excessive income probably diminishes the thyroid colloid. Administration of cod liver oil delays the metamorphosis of tadpoles; absence of the thyroid prevents the change of carotene to vitamin A. Administration of thyroid increases the consumption of *thiamine*. Administration of thiamine diminishes the loss of weight from thyroid administration, increases the pulse rate and temperature. The blood level of *pyruvic acid* is high in thyrotoxic patients. Deficiency of *ascorbic acid* produces thyroid hyperplasia (review, V. A. Drill, 1943).

Detoxification by Metals.—Administration of copper, 0.4 mg. per Kg., in any form, protects dogs and other animals against doses of thyroid which would otherwise be fatal in three to seven weeks. Iron is also quite effective; zinc, manganese and magnesium are much less so (Hesse *et al.*, 1933).

Increased metabolism is the most constant effect of thyroid administration. It occurs in normal animals, but is much more marked in the low metabolism of thyroid deficiency (DuBois, 1914). The heat production in Basedow's disease is also much above the normal. The metabolic effects of thyroid administration are shown by increased oxidation, increased consumption of oxygen and production of carbon dioxide, and increased excretion of nitrogen, with improvement of appetite and loss of weight (Leichtenstern, 1893). The first effect is on carbohydrates, then on fat, the proteins being drawn upon when the fat has been reduced to a certain minimum. Beginning after a latent period of twelve hours or more after administration is started, the heat production rises slowly; when the dosage is stopped, it declines as a logarithmic curve. From the latter, it may be estimated that thyroxin is destroyed in the body at the rate of 0.2 to 0.4 mg. per day (Plummer and Boothby, 1920). The increase of oxygen consumption may be used for the *assay* of thyroid preparations (Shackell, 1937). The increased need of oxygen renders thyroid-fed animals more susceptible to oxygen deficiency (Asher), and to the toxicity of drugs which increase the use of oxygen, such as dinitrophenol (Glaubach and Pick, 1934).

Thyroxin is necessary for the development of the *specific dynamic action* of foods, but the energy of the calorigenic action of thyroxin cannot be utilized in *muscular work* (Plummer and Boothby; Canzanelli *et al.*, 1934). *Hibernating animals* are awakened and kept awake by the administration of thyroxin (L. Adler, 1920; Schenk, 1922). *Dinitrophenol* also increases oxidative metabolism, but does not produce clinical improvement in myxedema. The time curve differs greatly from that of tyroxin, the metabolic rate reaching a maximum in two hours, in contrast with the three to ten days required with thyroxin. Its effects are not greater in thyroid deficiency, as are those of thyroxin.

The *site of the metabolic action* is not clear. It involves a peripheral effect, for oxygen consumption is abnormally high in excised tissues of thyroid-poisoned animals, or if the blood of such animals is added to liver tissue *in vitro;* not if thyroxin is added directly; but thyroglobulin is reported to be effective (Rapport, 1937; Craig and Salter, 1945). There is some evidence of a central action, probably on the *midbrain*, for the effect is much greater by cisternal than by hypodermic injection and much less in deep narcosis and in various brain lesions (von Issekutz *et al.*, 1937; Glaubach and Pick, 1935).

Carbohydrates.—It is doubtful whether the increased metabolism of carbohydrates is due chiefly to stimulation of oxidation, or whether it is an indirect result perhaps of increased *mobilization of liver glycogen* (Cramer and McCall). The glycogen store of the liver may disappear completely, even with food rich in carbohydrate, and without glycosuria. The glycogen of muscle disappears only if food is restricted (Bosl, 1928). There is evidence that excess of thyroxin causes severe degeneration of the liver in rabbits (Gerlei, 1933); the biliary elimination of injected sodium cholate is decreased (L. H. Schmidt, 1937), and Basedow patients often show more or less liver injury. It is claimed that thyroidectomized animals do not utilize sugar on parenteral administration as well as normal animals (Underhill and Saiki, 1908), and that they do not react with glycosuria to some of the procedures which are ordinarily effective (King, 1909). Cramer and McCall, 1918, found in rats that total removal of the thyroids and parathyroids does not impair the power of the cells to oxidize carbohydrates (as judged by the respiratory quotient).

The *increased oxygen consumption in excised tissues, muscle and glands* from animals to which large doses of thyroid had been administered seems to involve especially the anaerobic metabolism and is inhibited by cyanide (Rohrer, 1924; v. Euler and Enderlein, 1935; McEachern, 1935). It does not occur with cold-blooded animals, or not to the same degree (Drexler and v. Issekutz, 1935).

The **nitrogen excretion** is increased about 50 per cent in a five to seven day period (Rohde and Stockholm, 1919). Jamey and Isaacson, 1918, found the ratio of urea and ammonia to total nitrogen unchanged by administration of thyroxin. *Creatinine* excretion was unaffected, even when there was extensive tissue destruction. *Purine* excretion was diminished after excision and in cretins; increased after thyroxin and in Basedow's disease.

The urine volume and the water intake are materially increased in experimental hyperthyroidism. Fresh water intake is excreted more readily, protecting against water intoxication. The chloride of the excess urine is low. The protective action is largely abolished when the adrenals are excised (R. Gaunt, 1944). Clearance studies indicate that thyroid administration increases glomerular filtration in normal animals and in experimental diabetes insipidus; but the increase of urine output is as much as forty times greater in the operated animals, suggesting that hyperthyroidism renders the antidiuretic hormone less effective (K. Hare *et al.*, 1944).

Calcium Metabolism.—Administration of thyroxin increases the excretion of Ca and Mg (Auby, Bauer *et al.*, 1929) and lowers the plasma Ca level. The latter is increased in thyroid deficiency. Thyroid administration is reported to increase the proliferation and differentiation of retarded ossification (Silberberg and Silberberg, 1929), to accelerate bone calcification rate in young animals and to aid callus formation. The toxicity of *chronic fluoride administration* is increased by feeding thyroid, and conversely (Phillips, English and Hart, 1935). Further details of the thyroid and fluoride relation are discussed under Fluoride (see Index).

Use in Obesity.—Thyroid administration is often strikingly effective in reducing the fat in constitutional obesity (menopause, and so forth), much less so in superalimentation. The result is not permanent and is complicated by the sometimes dangerous effects described under overdosage. Only small doses should be used, under strict medical supervision. The protein income should be kept high to compensate the loss (v. Noorden, 1915).

Other Therapeutic Uses.—Thyroid has been tried in psoriasis, eczema, lupus, chronic rheumatism, gout, arteriosclerosis, rickets, infantile cachexias and hemophilia, but the inconstant results indicate that it is probably useless. Thyroxin administration increases hair growth in underfed rats (E. O. Butcher, 1940). It hastened somewhat the healing of wounds; dinitrophenol had a similar effect (T. H. Barclay *et al.*, 1944).

Larval Growth and Development.—Gudernatsch, 1912, observed that feeding of thyroid to tadpoles checks their growth, but at the same time hastens their development into frogs. This is a delicate test for thyroxin (Marine and Rogoff, 1916). The metamorphosis of axolotl and amblystoma is even more sensitive (B. M. Zawadowsky and Perlmutter).

This effect may be used for the *standardization of thyroid preparations* (Rogoff, 1917; Hunt, 1925). The susceptibility to the acceleration increases with the age of the tadpoles (Alphonse and Baumann, 1935; R. Geigy, 1944). It is also increased by exposure to x-rays (McCord and Marinus, 1918). It is antagonized by several ethers of N-acetyliodotyrosine (D. W. Woolley, 1946).

Other Thyroid Constituents and Iodized Products Tested by Tadpole Method.—Morse, 1914, found that the nucleoproteins, lipoids, and so on, of the thyroid are ineffective. Positive results are produced by iodothyrin, iodated tyrosine, iodized Witte's peptone and iodized serum proteins; not by inorganic iodine or iodides, iodized starch, iodized lecithin, or marine algae. The inefficiency of inorganic iodides, however, seems to be only quantitative, for their administration starts the metamorphosis of thyroidectomized tadpoles, which does not take place without this stimulus (Swingle, 1919). Allen, 1919, also observed that this does not occur if either the pituitary or thyroid is removed, but that it occurs in the absence of both glands if iodine is administered. The feeding of *other gland tissues*, yeast and foods in general influence the growth and somewhat the metamorphosis of tadpoles; but their effects are of different magnitude from those typical for thyroid feeding (Rogoff and Rosenberg, 1922). Feeding with *thymus* greatly delays the metamorphosis (Gudernatsch).

Acetylthyroxin accelerates the *development of newborn rats*, the differentiation of the skull, and so forth, but not the growth (Hoskins, 1927).

Protozoa.—The presence of thyroid tissue increases markedly the multiplication of paramecium (Nowikoff and Shumway; Budington, 1915).

Plant Growth.—Thyroid, when added to the culture medium, produces remarkable retardation of the root growth of onion bulbs. This effect is not produced by potassium iodide, nor by pituitary or suprarenal (Budington, 1919).

Susceptibility of Poisons.—The metabolic disturbances alter the destruction of poisons in the body. In mice, *f. i.*, the toxicity of acetonitrile is greatly diminished, while that of morphine is increased. The toxicity of thyroxin itself is greatly influenced by the diet (W. Kornfeld and Nobel, 1928).

Acetonitrile Test.—Hunt (1905, 1907, 1908) found that the administration of thyroid to white mice, for a few days, markedly increases their resistance to acetonitrile. The toxic effects of the latter are due to the liberation of HCN. Thyroid feeding does not affect the toxicity of HCN when administered as such, so that its protective influence must be due to a retardation of the metabolic processes which convert acetonitrile into HCN. In rats and guinea pigs it has the opposite effect, increasing the toxicity of the nitriles. The acetonitrile response is a nearly specific test by which 1 mg. of active thyroid tissue can be detected. Thyroid in which no iodine can be detected by the ordinary chemical tests, as well as certain other organs, show a very feeble activity (Hunt and Seidell, 1908). Trendelenburg, 1910, and Lussky, 1912, reported that the blood of cats gives the test even after removal of the thyroids. Application of the test to the blood of Basedow's disease has not given conclusive results. Certain *diets*, dextrose, oatmeal, liver or kidney, also increase the resistance of the mice to the nitrile, as compared with cracker, milk, cheese or egg diet. This seems to be due to an action on the thyroid, for the difference is diminished if the thyroids are excised; and these glands present anatomic changes (Hunt, 1910, 1911). *Other iodine compounds* have some protective action, presumably by being converted into the thyroid compound. None reach the same activity, but they present interesting differences. The iodine of the seaweed, bladderwrack, is about one hundred times as active as the iodine of potassium iodide (Hunt and Seidell, 1910).

Cyanide metabolism has complex relations with thyroid function. If acetonitrile is fed to normal rabbits, 25 per cent or more of its CN is excreted in the urine as SCN;

but only 3 to 5 per cent with animals whose thyroid has been removed. This also decreases the conversion of potassium cyanide into thiocyanate, but only temporarily (E. J. Baumann, Sprinson and Marine, 1933). Acetonitrile materially augments the goiterogenic action of cabbage and of alfalfa hay for rabbits, and this is prevented by feeding traces of iodine (Marine, 1935).

Acetylation of sulfanilamide is decreased by thyroid administration and hyperthyroidism, and increased by thiouracil (J. Fraenkel-Conrad and Greenberg, 1946).

Synergism with Amino Acids.—Kendall, 1916, 1917, found that thyroxin alone produces symptoms analogous to those of exophthalmic goiter, but has no direct effect on the pulse rate, even on intravenous injection. If, however, amino acids are injected at the same time, there are marked disturbances of the pulse rate and of metabolism, which may be fatal.

The *methylation of guanidineacetic acid to creatine* is prevented in rabbits by removal of the thyroid glands, and restored by administering iodine (Stuber, Russmann and Pröbsting, 1923).

Resistance to Morphine Alkaloids.—Thyroxin administered to mice, rats and guinea pigs lowers their resistance to morphine (Hunt). With mice this holds also for heroin, but not for codeine and thebaine (Anan, 1929). The phenomenon probably involves the oxidation of the side chains. The morphine sedation tends to protect rats against the increased oxygen demand of thyroxin, so that it renders thyroid-poisoned rats more resistant to oxygen deprivation (Asher *et al.*). *Clinically, myxedemic patients and cretins are oversusceptible to morphine* (Lund and Benedict, 1929), presumably by the summation of the two lethargies.

Quickening of the heart rate is a constant symptom of experimental hyperthyroidism and of Basedow's disease. With thyroid-poisoned rabbits the acceleration persists when the heart is excised and perfused, and in auricular segments, which beat some 50 per cent faster than normal heart preparations. The acceleration therefore is directly cardiac (Andrus, 1932). The excised heart of normal rabbits, however, is not affected by the direct addition of thyroxin; but this does increase the response to epinephrine (Asher *et al.*, 1916). The response of the intact thyrotoxic heart to epinephrine and to mecholyl is much greater than normal (B. Wise and Hoff, 1938).

The change of heart rate is *not due to change of metabolic rate*, for while thyroxin administration quickens the heart of thyroidectomized rats, dinitrophenol fails to do so. Diiodotyrosine also lacks this effect (C. P. Leblond and Hoff, 1944).

The *direct effects on the circulation* vary, and are probably indirect, owing to increased excitability of the sympathetic and parasympathetic nerves (Oswald, 1915). Intravenous injection of thyroid extracts usually produces fall of blood pressure and slowing of the heart, probably owing to its choline content (Fuerth, 1909; Schoenborn, 1909). The response of the heart to *vagus stimulation* is not affected by thyroid (R. L. Levy, 1918). Complete excision of the thyroid-parathyroid apparatus lowers the vagus excitability (Coronedi, 1913).

Thyroidectomy in Congestive Heart Failure.—Lowering of the metabolism decreases materially the demand on the heart, and total thyroidectomy results in marked and lasting improvement in a number of cases. With partial ablation, the improvement is only temporary. The operation is a last resort in angina pectoris, especially when other therapy has failed (Blumgart and associates, 1933). It generally results in temporary parathyroid tetany and sometimes in excessive thyroid deficiency symptoms, which must be treated in the usual manner; the thyroid deficiency by minimal doses, 8 to 15 mg., of dried thyroid daily (Means, 1934).

Secretion of cerebrospinal fluid is said to be inhibited by thyroid and increased by brain extract, independent of blood pressure changes. Other organ extracts act only mechanically, through the circulation (Frazier and Peet, 1915). *Bile secretion* is not affected by thyroid administration (Downs and Eddy, 1919).

Sensitization to Autonomic Stimulation.—Injection of thyroid does not produce any characteristic autonomic stimulation directly, but it increases the response to epinephrine, splanchnic and depressor stimulation (Blau and McNamara, 1930); also after removal of the adrenal glands (Bergwall and Kuschinsky, 1931). Thyroid administration likewise increases the depressant action of histamine (Oswald, 1915). Conversely, removal of the thyroid gland diminishes the sympathetic response to epinephrine and greatly increases parasympathetic irritability, *f. i.*, to choline; feeding of thyroid restores the responses to normal (Schliephake, 1928). Patients with Basedow's disease sometimes give alarming reactions to epinephrine. This, however, may involve mechanisms other than the peripheral autonomic sensitization.

The peripheral sensitization to epinephrine is situated at the receptive mechanism (Asher, 1916). The symptoms of *cocaine* poisoning resemble those of "hyperthyroidism," since both involve sympathetic stimulation. There is no causal connection. Oft-repeated injections of cocaine do not produce any histologic changes in the thyroid (Mills, 1919). The *motility of the gastro-intestinal tract* is increased by thyroxin administration, and the hunger contractions become stronger (Fetter, Barrow and Carlson, 1932).

The **anterior pituitary interrelation** appears to be the mechanism for the adjustment of the thyroid function to the regulation of the oxygen metabolism to physiological needs. The anterior pituitary thyrotropic hormone is the only agency known to stimulate the thyroid acini directly to increased production of thyroxin; and conversely, thyroid deficiency stimulates the anterior pituitary to the production of more thyrotropic hormone, to compensate for the deficiency (reviews, Loeser and Thompson, 1934; Marine, 1935).

Excision of the thyroids leads to hypertrophy of the anterior pituitary (Rogowitsch, 1889), especially in young animals. The most striking change is the disappearance of the eosinophilic granules from the oxyphile cells. Conversely, *removal of the hypophysis* leads to involution of the thyroid (Smith), with a colloid type of goiter. This is restored by the injection of anterior pituitary extracts, but not by the administration of iodine, indicating that thyroxin is not synthesized in the absence of the thyrotropic hormone (Loeser and Thompson, 1934). In normal animals, *injection of the thyrotropic hormone* which has been separated from the growth and sex hormones, results within twelve to twenty-four hours in congestion of the thyroid and hyperplasia with diminishing colloid, decrease of the thyroid iodine store, increase of the blood iodine, increased excretion of calcium and creatine and the phenomena of hyperthyroidism or rather Basedow's disease, including exophthalmos. Daily hypodermic injection doubles the thyroid weight of guinea pigs in three to six days. If the hormone injection is stopped, the histologic and functional picture returns to normal. The phenomena do not occur after removal of the thyroid (L. Loeb *et al.*, 1931; S. Hertz and Roberts, 1941). The response of the thyroid to thyrotropic hormone decreases with continued administration. Collip and Anderson, 1935, attributed this to the production of an *antithyroid hormone*, which inhibits the formation of thyroxin. The response to thyroxin is not impaired.

Thyroid interrelations with gonadal functions are indicated by the goiter tendency at puberty and in pregnancy and estrus. They are presumably mediated through the anterior pituitary (Marine, 1935). Thyroxin administration to lactating animals increases the yield of milk and its fat content; but the thyroid is not essential to initiation of lactation (references, W. E. Petersen, 1944). Thyroxin interferes with the action of estrogen in pigeons as to increase of plasma Ca, P and lipid, but not as to endosteal bone and oviduct growth (M. R. McDonald *et al.*, 1945). Its administration to aged fowl produces apparent *rejuvenation* with increased egg production (Crea, 1924; C. W. Turner). It is also reported to increase the fertility of old rams (cited by S. Brody, 1946). Excision of the thyroid of hens causes marked decrease of *egg production*, which is largely restored if thyroxin is administered (C. F. Winchester). *Plumage changes* are characteristic: The administration of thyroxin to chickens causes changes in the feather-forming cells, leading to the accumulation of dark pigment in the portion of the feathers formed during this period (L. J. Cole and Reid, 1924). A single hypodermic injection produces the effects in the feathers of a plucked breast area in roosters, perceptible in a day and lasting five days. The response is quantitatively proportional to the dose and may be used for assay. It is not given by other iodine derivatives, nor by sex hormones and other organ extracts (Juhn and Barnes). Other effects of thyroid administration are described by Zawadowsky and Titajev, 1928; J. H. Martin, 1929; and Hutt, 1930.

Innervation of Thyroid.—The gland is supplied with nonmedullated fibers, probably derived from the cervical sympathetic, and going to the cells as well as to the blood vessels. An action current develops in the gland on stimulation of the sympathetic, high in the thorax, even when the superior and recurrent laryngeals have been cut. Vagus stimulation or pilocarpine does not generate the action current (Cannon and Cattell, 1916). On the other hand, autografts of thyroid show evidence of growth and function, so that the nervous connections are not indispensable (Manley and Marine, 1916).

Epinephrine on Thyroid Secretion.—Injection of epinephrine, 0.001 to 0.002 mg., evokes an action current in the thyroid. The same result follows stimulation of the cut splanchnic, but it is absent if the adrenal blood is prevented from reaching the circulation (Cannon and Cattell, 1916). *Thyroxin injection* was reported to increase the secretion of epinephrine after twenty to forty-five minutes (Zunz and La Barre, 1932)

Thyrotoxicosis.—The phenomena of Basedow's disease bear a striking resemblance to those of overdosage with thyroxin, particularly the increased metabolic rate and the hypersusceptibility to sympathetic stimulants. The symptoms are promptly controlled by partial or complete excision of the gland, or by administering *thiouracil*, thiourea, or related sulfur-containing chemicals (see Index). The thyroid is commonly enlarged, but the structural changes need not be great and do not differ from those of nontoxic goiters (Marine, 1911). The change is therefore functional, presumably by overstimulation through anterior pituitary thyrotropic hormone, in response to some unidentified factor, perhaps related to the sex glands (but not estrogenic hormone) or to the adrenal cortex. This may occur when the iodine income appears ample. Administration of iodine in any form decreases the phenomena, however, at least temporarily, perhaps by checking the excessive drive for thyrotropic hormone. Simple iodine deficiency probably also increases the production of pituitary thyrotropic hormone, and results in thyroid hyperplasia; but the toxic factor is lacking, presumably because the drive is not so intensive. The output of thyroxin is limited to the available iodine.

Increased Metabolism in Basedow's Disease.—Heat production is 50 per cent above the normal in severe, and 75 per cent in very severe cases. The excessive heat production accounts largely for the tachycardia, cardiac enlargement, emaciation and mental irritability. Rest in bed for a week diminishes the excessive heat production by 10 per cent or more; psychotherapy was also of some value. The high metabolism means that the patients need one and one-half to two times as much food as normal individuals (Means and Aub, 1919).

The *exophthalmos* is not due to thyroxin, for it can be produced more easily after excision of the thyroid (Marine and Rosen, 1934), by administering thyrotropic hormone (E. Shorr, 1944). It involves swelling of the extraglobular contents of the orbit, including the extrinsic muscles (J. H. Means, 1944).

The *iodine metabolism in Basedow's disease* presents some quantitative anomalies. The thyroid glands are poor in organic iodine. The *negative balance* on low iodine income is two or three times greater than in normal individuals, and on administering iodine, the positive balance is correspondingly greater than normal. The *iodine level of the plasma* is 0.009 mg. per 100 cc., over twice the normal. The increase is chiefly organically combined, presumably thyroxin. The urine and feces are also richer in iodine. After partial excision of the gland, or with successful medical treatment, the abnormalities return to normal (Puppel and Curtis, 1938).

Iodine Therapy of Toxic Goiter.—The continued administration of moderately large doses of iodine or iodide produces marked and specific amelioration of all the symptoms (Plummer, 1923). The beneficial effects increase progressively for ten to twenty days. The nervous tension relaxes, the sleep and appetite improve, the tachycardia is markedly slowed, the excessive metabolic rate is diminished by 25 to 30 per cent and the patient gains in weight and strength. This amelioration is a cardinal feature of Basedow's disease and is practically pathognomonic for diagnosis, prognosis, and treatment. The more severe the "toxic" symptoms, the greater is the improvement under the iodine. The improvement does not arrest the progress of the disease, but merely keeps it at a lower level, and after some weeks the metabolism tends again to rise and the symptoms to return gradually even if the iodine is continued. If the administration is stopped, the condition relapses in a week or two to the state which it would have reached without the iodine. The method is therefore used mainly to prepare patients for surgical treatment: the sedative effect diminishes the surgical risk, especially by protecting the patients against a critical reaction to the fear and excitement of the operation and to the postoperative discomfort. The convalescence is also shortened (Means and Lerman, 1935). All forms of iodine are effective, and sodium iodide is as good as any. Even the administration of dried thyroid (2 grains per day) lowers the metabolic rate of toxic patients (Rice and Cavett, 1934, by depressing the response of the thyroid to thyrotropic hormone (R. Cortell and Rawson, 1944). The mechanism of the action of iodine is not clear; the most plausible explanation is that the iodine diminishes the overproduction of thyrotropic hormone.

The administration of iodine in toxic goiter had been suggested by Marine, 1911, because the structure of the gland in many cases suggested iodine deficiency. He advised, however, that this should be practiced cautiously, lest it lead to an overproduction of thyroxin by the hyperplastic glands, before involution had set in. This fear prevented adequate clinical trials of the suggestion until it was reintroduced in a modified form by Plummer, 1923.

In experimental Basedow disease, produced in guinea pigs by the injection of an alkaline extract of anterior pituitary, the high metabolic rate was decreased and death prevented by the administration of sodium iodide (Friedgood, 1935; Trikojus, 1939). The *thyrotropic hormone* in the anterior pituitary gland of normal animals was reported diminished by small, and increased by large, doses of iodide (Loeser, 1934).

Dosage.—Potassium or sodium iodide is administered for one to three weeks before and for a week or two after the operation. They are usually prescribed as a saturated solution, 5 to 10 minims once daily, equivalent to 0.25-0.5 Gm.; but 9 to 15 mg. suffice (E. Shorr, 1944). Other preparations and complicated technics have no advantage (Means, review, 1935).

Plummer originally employed 0.5 cc. of Lugol's solution in milk, one to three times daily. W. O. Thompson, Brailey *et al.*, 1930, showed that 6 mg. of iodine per day suffice to produce the maximal reduction of basal metabolism in Basedow patients; smaller doses caused proportionately less reduction.

Toxic effects from iodide administration, by the provocation of toxic hyperthyroidism, have been claimed for various forms of goiter, especially adenomatous (Boothby and Rowntree, 1923; Oswald, 1915). The evidence is not convincing. Administration of iodine does not produce hyperthyroidism, even when the plasma level of iodine is raised to 7 mg. per 100 cc., about six hundred times the normal level (Curtis, 1935). However, severe acute iodism, sometimes febrile, may occur with large doses of iodine, and may or may not recur with subsequent administrations (W. H. Barker and Wood, 1940).

Radioactive iodine is being tried as a means of selective introduction of destructive radioactivity into the thyroid gland. Oral administration of a single dose of sodium iodide to thyrotoxic patients has produced permanent remission, without other effects. It is most effective if the accumulation is not hampered by preceding iodine mediation. The advantages and dangers are not yet sufficiently known (S. Hertz and Roberts, 1946; E. M. Chapman and Evans, 1946).

Thyroid Deficiency.—The results of excision of the thyroid gland are essentially the opposite to those of hyperthyroidism; *i. e.*, they consist in diminution of the basal metabolism and sluggishness of the nervous processes. When the parathyroids are also removed, these phenomena are complicated by parathyroid tetany. Continued thyroid deficiency, when occurring in adults, results in *myxedema*, with conspicuous skin changes and nervous disturbances ending in mental deterioration. Congenital deficiency produces the condition of *cretinism*, stunted physical development and idiocy.

Complete excision of the thyroid apparatus causes a series of effects, motor, nervous and metabolic (cachexia strumipriva), which are more or less rapidly fatal for most animals, especially for carnivora. If the parathyroids are spared, the motor symptoms and the fatality are much less, and the metabolic disturbance runs a more chronic course. These phenomena were first described by Schiff, 1856. The *lowered heat production* of thyroid deficiency was first shown clinically by Magnus-Levy, 1895. In most mammals the fall begins on the fifth to seventh day after the excision. In rabbits it reaches its minimum (30 to 40 per cent) between the twentieth and thirtieth days, in man about the sixtieth day. This minimum level may then be maintained for years. Such animals have a low basal metabolism with high respiratory quotient. They are hypersusceptible to oxygen deficiency (Hildebrandt, 1922). If fragments or accessory thyroids are left, the condition may gradually return toward normal. The *cutaneous myxedema* which develops in adults is due chiefly to intracellular fluid.

Thyroidectomy for the treatment of congestive heart failure was introduced on the basis that the slowed metabolic rate diminishes the demands on the circulation, especially in angina when other measures have failed. The majority appear to be more or less improved, but only if the excision is complete. The parathyroids are generally also removed. The tetany is usually transient, but the myxedematous changes progress, requiring constant treatment with thyroxin, keeping the dosage below normal (review, Parsons and Parks, 1937).

Experimental Cretinism.—Complete thyroidectomy in young animals is followed by typical cretin phenomena, such as dry, rough hair, retarded growth, skin changes, and so forth (Basinger, 1916). The long bones grow more slowly and stop before they reach the normal length. The nervous and skeletal systems are relatively large, the viscera small, in proportion to the total body weight (Hammet, 1929).

Therapeutic Results of Thyroid Feeding.—The deficiency symptoms are completely relieved in adults by the administration of thyroid or thyroxin by mouth (Howitz, Mackenzie, Fox, 1892), as well as by intravenous injection (Colzi, 1884), of thyroid extracts, or by implantation of thyroid tissue (Schiff, 1884). In cretins, the improvement depends on the age when the treatment is begun, and on the intensity and persistence of the treatment. Most cretin children remain more or less retarded, mentally and physically, but many are at least improved (A. W. Brown *et al.*, 1939). The *administration* must be practically continuous and the dosage must be carefully adjusted to avoid toxic effects. It is sufficiently attained by the oral administration of the dried gland. This may be taken as tablets or in capsules. The proper *dosage* must be determined by trial. In *myxedemic adult patients*, the daily ration should be the minimum that keeps the patient free from symptoms. For this it is rarely necessary to raise the metabolic level above minus 20, which is attained with 60 to 180 mg. (1 to 3 grains) of dried thyroid or 0.2 to 0.4 mg. of thyroxin once daily, and sometimes with less. The dosage may be lower in summer than in winter. The response is striking; in a few days the patient feels warmer and less sleepy, the muscular movements and speech are faster, the sensorium is more alert, the cutaneous edema disappears, with diuresis and desquamation of the skin, the hair texture returns and in two weeks the patient becomes practically normal (Means, 1934). The first warnings of overdosage are sometimes myalgia and anginal attacks, but patients with thyroid deficiency tolerate larger doses than normal subjects. The *treatment of cretins* requires relatively large doses to permit normal growth. Unless this is started within the first two years of life, the stunting of the mental and bodily growth cannot be completely repaired, and in older cretinous imbeciles the results are often disappointing.

Isolated thyroxin does not have sufficient advantage for oral administration over the standarized U.S.P. dried thyroid to offset its much higher cost, except for scientific investigation. Orally or intravenously, 1 mg. of thyroxin is therapeutically equivalent to 0.2 Gm. of desiccated thyroid. Its dosage is 0.2 to 2 mg. daily, starting with the minimal doses and increasing if necessary as judged by the basal metabolic rate. High grade cretins require 1.5 to 2 mg. daily. Crystalline thyroxin, natural or synthetic, may be given *intravenously* in the occasional emergencies when it is not absorbed orally. It is dissolved by careful addition of alkali. *Synthetic Thyroxin Solution* is marketed in ampuls of 1 cc. containing 1 mg.

Thyroxin Requirements.—Means and Aub, 1919, found that the basal metabolism in hypothyroidism is restored to normal by daily doses starting with 0.2 to 0.25 Gm. (3 to 4 grains) of the dried gland, and later 0.05 to 0.1 Gm. (1 to 2 grains). According to Plummer and Boothby, 1920, the total need of the body for thyroxin lies between 0.2 and 0.4 mg. per day, as calculated from the "decay curve," which would be supplied by 0.065 to 0.15 Gm. of the U.S.P. thyroid powder. With synthetic (racemic) *thyroxin*, H. Baur, 1928, found that toxic symptoms resulted from 3 to 4 mg. per day for some weeks; but 1 to 2 mg. per day for a limited period increased the basal metabolism of normal individuals by 140 per cent, without toxic effects. There was also marked increase of water elimination. Individuals with high basal metabolism showed a relatively smaller increase, 10 to 37 per cent.

Differences in commercial thyroid preparations may exist even when the total organic iodine content is similar, since only the thyroxin part of this is active. Practically, however, they do not appear very significant.

Lerman and Salter, 1934, found the total organic iodine of six preparations to range from 0.22 to 0.40 per cent of the dried thyroid, and 16 to 42 per cent of this iodine was thyroxin. However, the calorigenic effect on myxedema patients was in reasonably close agreement.

PREPARATIONS.—*Thyroid, U.S.P. (Thyroideum), is the dried and powdered healthy thyroid glands of domestic animals used for food, containing about 0.2 per cent iodine in thyroid combination. One part of the dried corresponds approximately to five parts of the fresh gland. Dose, 60 mg., 1 grain. It is usually administered as *Thyroid Tablets*, U.S.P., containing 15, 30, 60 or 120 mg.; ¼, ½, 1 or 2 grains. Raw or broiled glands (⅛ to ⅓ gland) have also been used, but have no advantage. *Thyroxin*, U.S.P., prepared from glands or synthetically, contains not less than 64 per cent of iodine. White needle-like crystals or powder, insoluble in water, soluble in alkalis. Average dose, 0.5 mg., 1/120 grain.

GOITER PROPHYLAXIS

Endemic Goiter.—In regions distant from the sea and from other deposits of iodine, the income of iodine through food and drink is limited and tends to become inadequate when the demands for thyroid secretion are high, especially in adolescent girls. This leads to excessive proliferation of the thyroid epithelium, perhaps through futile efforts to compensate for the iodine deficiency. This hyperplasia is the first stage of "*endemic goiter.*" If the excessive demand ceases, or if the deficiency is met by the administration of an iodine compound, the hyperplasia stops, the acini become filled with colloid, and the goiter changes to the resting, relatively harmless but deforming "colloid" type. Repetition of the iodine deficiency causes this to revert again to the hyperplastic type, which may again become more colloid, and so on (Marine, 1907 to 1913; review, 1935). The hyperplasia indicates increased activity of the thyroid gland, but not necessarily increased production of thyroxin; indeed, myxedema and cretinoid states may occur in the presence of hyperplasia.

Thyroid hyperplasia is characterized by increased blood supply, decreased colloid and iodine content of the acini, change of the follicular epithelium from low cuboid to columnar, mitoses, infoldings and formation of new follicles. *Transplanted thyroid tissue* reacts in the same manner, by hyperplasia or involution, to removal of thyroid tissue or to iodine; so that the changes are evidently independent of the nerve supply (Manley and Marine, 1915). If the hypertrophy is inadequate to meet the demands, the acini may finally *atrophy*. This occurs also if the anterior pituitary is removed, and in Gull's disease. Thyroid function and structure may then be restored by the injection of thyrotropic hormone.

The *etiology of the hyperplasia* may be conceived as a compensatory hypertrophy initiated through the anterior pituitary thyrotropic hormone in response to the demand of the organism for a larger supply of thyroid secretion. It may be produced experimentally by injection of the hormone, by removal of a part of the thyroid gland, by certain diets and by deficiency of iodine income. It may occur in any locality, but is much more frequent in certain regions (*endemic goiter*). It is most likely to develop clinically during fetal life; at puberty, especially in girls of ten to sixteen years; in pregnancy and lactation; and at the decline of sexual life. Its *geographical distribution* appears in relation to glacial formation, perhaps through leaching of the soluble minerals. It has been blamed especially on the water supply, since Pliny. The most important factor seems to be low iodine content, then high calcium content. The food raised in such regions is also poor in iodine. In some goiter regions, however, the iodine of the food and water is not below normal, and the iodine excretion by urine is abundant (L. Scheffer, 1932). The *iodine factor* will be further discussed below. Other agents that tend to induce goiters are calcium salts, cabbage and cyanides.

The *calcium factor* is not understood. With constant iodine income, increase of calcium income results in thyroid enlargement (J. Thompson, 1933); hyperplastic if the iodine income is low, colloidal if it is high (Hellwig, 1935). The response to thyroxin is decreased (Abelin, 1928). Calcium also retards the acceleration of tadpole metamorphosis by thyroxin (Zondek and Reiter, 1933).

The *calcium balance* in its turn is altered by the thyroid. Calcium excretion is increased in Basedow patients and diminished in myxedema (Aub). Hyperplasia by cabbage diet leads to calcium retention, which is removed by administering iodide. Phosphate and magnesium parallel the calcium; K, Cl and N are not changed.

Dietary thyroid hyperplasia is produced in dogs by fresh *meat* (Baumann, 1896), especially *liver* (Marine and Lenhart); by fats (McCarrison, Mellanby); and in rabbits by *cabbage* (Chesney *et al.*, 1928; F. Blum, 1942). *Inanition* causes involution of the thyroid (E. J. Baumann and Hunt, 1925).

Cyanide Relation.—The effects of *cabbage* and other cruciferous plants are due to the presence of nitriles. Other nitriles, especially acetonitrile, and inorganic cyanides also produce thyroid hyperplasia and exophthalmos, if the dosage is properly adjusted. It is conceivable that the thyroid stimulation is an attempt to overcome the cyanide depression of oxidative metabolism; since cyanide is a normal product of cell metabolism, it is tempting to suppose that thyroxin and cyanide serve to adjust and preserve the proper oxidation balance of the organism (Marine, 1932).

A *fluoride relation* was postulated by Maumenèe, 1866, and the theory has been revived by Goldemberg (see Index, Fluoride), but it has not been confirmed by others.

An organic *selenium* compound also produces rapid thyroid hyperplasia, and adenomatous changes in the liver (J. Seifter, Ehrich *et al.*, 1946).

Iodine Prophylaxis.—Simple goiters are conditioned on absolute or relative deficiency of iodine, and Marine showed that they can be prevented, arrested and to some degree cured, by the administration of small quantities of iodine, in any form. Goiters that supervene with iodine income which would ordinarily be adequate are cured by increasing the iodine income (Oswald, 1927). In goiterous regions endemic hyperplasia may be expected to occur in some degree in adolescent girls and in pregnancy, unless iodine is administered; as the early stages are not easily recognized, it is advisable to administer iodine as a routine, at these periods. Hyperplasia occurs also under other conditions in both sexes and at any age, forming a fruitful soil for the development of serious thyroid diseases. It would therefore be advisable to make iodine prophylaxis universal in goiter regions. The clinical success was first conclusively demonstrated through mass prophylaxis by iodine in the brilliant results reported by Marine and Kimball, 1917, 1918, 1920, for large groups of school girls in the Lake Erie goiter district. The administration of iodide prevented the appearance of goiter in over 99 per cent of the girls and diminished the size of the thyroid in most cases where the gland had been enlarged before medication. Iodide rash occurred in less than 0.5 per cent and was always mild. None developed any symptoms of hyperthyroidism. Similarly beneficial results were obtained in the goiter districts of Switzerland. At St. Gall the weekly administration of an organic iodine compound to the children reduced the goiter incidence from 88 to 13 per cent. Established goiters in girls up to fifteen or eighteen years of age may disappear under treatment, but rarely after the twentieth year (Silberschmidt).

The fear that the promiscuous use of iodine would convert simple and especially adenomatous goiters into toxic goiters, appears to be unfounded. No instance of this has been reported with the weekly dose, if this did not exceed 10 mg. of iodine; nor has it ever occurred in school children even with the more intensive but brief dosage of Marine and Kimball. It is doubtful whether it ever occurs even with larger doses (Means). Unnecessarily large doses are inadvisable, however, on the ground of iodism.

Historical.—Iodine in the form of sea water, sea salt, seaweed or burnt sponge appears to have been used against goiter by the ancient Chinese, Egyptians, Greeks and Romans. Soon after iodine was discovered, it was used against goiter by Coindet (1820), but without thought of supplying a deficiency. This explanation was advanced by Prévost in 1849 and elaborated by Chatin, 1850. The latter believed that endemic goiter and cretinism could be avoided by the continued administration of small quantities of iodine, by the selection of foods relatively rich in iodine, and by iodized table salt, which had been suggested for this purpose by Boussignault in 1833. Modern use of iodized salts dates from Wagner von Jauregg, 1898.

Iodine Income, Requirements and Storage.—The daily income of iodine differs materially in goiterous and nongoiterous regions. The iodine salts that occur in the soil are easily leached out, so that the soil water can contain notable amounts of iodine only if this is being constantly renewed, by diffusion or spraying from the ocean or by the vicinity of considerable iodine-salt deposits. These geographic and geologic relations are reflected in the distribution of endemic goiter. The iodine content of the springs, rivers and lakes of goiterous regions ranges generally between 1 and $22:10^{11}$, that of the nongoiterous regions lies between 23 and $18{,}000:10^{11}$. The median iodine content of the waters of the nongoiterous is 145, that of the goiterous $6:10^{11}$; *i. e.*, about $\frac{1}{25}$ of the normal. Water bodies contaminated by the waste of large cities may have their iodine content considerably increased; for instance, the iodine content of Lake Erie at Cleveland is $86:10^{11}$, although this lies in the goiter belt. The *iodine content of the water* is important but not through the amount of water consumed directly, as food or drink; for a liter of $100:10^{11}$ represents only 0.001 mg. The real importance of the iodine in the water is that it determines the *iodine content of the foods* raised in the region. All plants and animals and therefore practically all natural foods contain small quantities of iodine. The content varies materially in goiterous and nongoiterous regions.

McClendon and Hathaway, 1924, for instance, found that carrots grown in the goiter belt of Oregon contained only $\frac{1}{75}$ as much iodine as those grown on the California coast; the iodine content of oats from Minnesota was $\frac{1}{15}$ that in Maine. Wheat is low in iodine; relatively rich are fruits, leafy vegetables, whole milk and butter and animal foods (Fellenberg, 1923).

The *correlation of goiter with iodine deficiency* is illustrated by the studies of McClendon and Holridge, 1935, of the two geological regions of Minnesota. The glacial Northeast has twice the incidence of goiter. Its drinking water contains much less iodine, (0.01 ppm, as against 0.05 to 0.14) and its vegetables about half as much as in the Western region. The *protective value of foods* when added to a low iodine diet of rats depends practically altogether on their iodine content, a given amount of iodine being equally effective as it occurs in milk, oysters or fish, or as KI. That of Irish moss is less effective (R. E. Remington *et al.*, 1936). In *plants*, iodine is more abundant in the leaves. It is increased by enriching the soil with iodine, but depends partly on the physical condition of the soil and its Ca and acid content (von Fellenberg, 1926). The *proportion of iodide in sea water* is only a millionth that of chloride, but it is greatly concentrated in marine organisms. Sponges contain up to 1.5 per cent of their dry substance. Cod liver oil contains 0.16 to more than 0.32 per cent, evidently in liposoluble form. Seaweeds (kelp) are a commercial source of iodine, and some may be present as the free element, for the vacuole juice of certain algae of the Gulf of Naples colors starch blue (Golenskin and Robertson). It contains an iodoxidase which liberates iodine from iodides (O. Gertz).

The *actual total income of iodine in the normal diet* of the Minnesota goiter region was determined by McClendon and Hathaway, 1924, as 0.019 mg. per day. For Switzerland, the iodine income for a goiter region was estimated by von Fellenberg, 1924, as 0.014 mg. per day; for a nongoiter region as 0.031 mg. per day, *i. e.*, about twice as high. The actual difference, however, is less than 0.02 mg.! From all the available data, it may be estimated that the daily requirement of iodine is of the order of magnitude of 0.03 to 0.05 mg. of iodine, or 10 to 20 mg. per year. This is about half of the total iodine content of the body, which is therefore replaced in two years. This shows great efficiency in the iodine economy: since the destruction of thyroxin approximates 0.2 to 0.4 mg. per day, equivalent to 0.13 to 0.27 mg. of iodine, and the daily diet need supply only 0.03 mg. of iodine, four-fifths of the iodine of the destroyed thyroxin must be reconstructed into thyroxin.

From the Swiss experience, Eggenberger, 1935, estimates the daily requirement as 0.001 to 0.002 mg. per Kg. of body weight. Below 0.001 there is danger in any region; with 0.002, there is no danger, even when susceptibility is increased by infection or by unsuitable diet. It is generally believed, however, that a daily income of 0.05 mg. (*i. e.*, somewhat less than 0.001 mg. per Kg.) gives a satisfactory margin of safety for normal individuals.

The total iodine content of the normal human adult ranges between 20 and 50 mg. At least a fifth of this is in the thyroid gland, half in the muscles, a tenth in the skin, a seventeenth in the skeleton, less than a tenth in the blood. The iodine concentration in the thyroid, at least 40 mg. per cent, is more than a thousand times that of muscle (30 gamma per cent). The next highest concentration is in other endocrine glands, up to about 100 gamma; blood contains about 10 gamma per cent (review, Salter, 1940).

Iodine Balance.—Puppel and Curtis, 1938, reported that normal persons on a diet low in iodine, 0.029 mg. per day, excrete 0.071 mg., giving a negative balance of 0.042 mg. Swiss reports, however, claim that a positive balance may be maintained with as low as 0.017 mg. In the latter case, about 0.014 mg. is excreted, about four-fifths by the urine. With incomes of 0.055 to 0.075 mg., the maximal retention was 0.02 mg. (von Fellenberg, 1926; Scheffer, 1933).

Iodine Storage in the Thyroid Gland.—Iodine administration may raise the iodine content to 4 mg. per Gm. of dried thyroid; *i. e.*, to 20–30 mg. in the whole normal gland of man. This represents an excess of 10 to 20 mg. over the normal content of 10 mg., as was explained in the preceding paragraph. The excess is sufficient to supply the iodine needs for half a year or a year; this explains the persistent effect of the periodic iodine medication, as in the method of Marine and Kimball.

Administration for goiter prophylaxis is especially important with girls between eleven and sixteen years; and during pregnancy. The iodine may be administered daily; or by taking advantage of the storage capacity of the glands, the administration may be made intermittent, *i. e.*, weekly, monthly or semiannually. Both the intermittent and continuous methods are effective in practice, so that the choice may be determined by convenience, or rather, by the faithfulness with which the prophylaxis is likely to be carried out. Iodized salt is preferable for community prophylaxis. For groups or individuals the intermittent methods can be more effectively supervised, and are therefore generally preferable. They require a large dosage, to insure "saturation" of the glands, but this is not a serious disadvantage when the administration is intermittent. The compound in which the iodine is administered is immaterial for the effect. The organic forms can be made into tasteless or flavored tablets, and are therefore usually preferred for the weekly dosage. They are not so well suited for the larger doses needed in the intensive semiannual method.

Semiannual Method.—In their decisive experiments, Marine and Kimball administered sodium iodide twice a year, in May and December, in courses of ten days each. Up to ten years, the daily dose was 0.2 Gm., from ten to sixteen years, 0.4 Gm., taken in a little water. This plan has been continued in many of the American schools which practice goiter prophylaxis, and the results have not been surpassed by any other method. The lower dosage is probably more than sufficient, for it supplies 0.170 Gm. of iodine per day, 1.7 Gm. during the course and 3.4 Gm. during the year, two hundred times as much as the safe daily income of 0.05 mg.

The *weekly method* was introduced in Switzerland and has given equally good results. It administers 5 or 10 mg. of iodine, one day each week, usually in the form of tablets of *organic iodine* such as iodostarin, each tablet containing 10 mg. of iodine, although sodium iodide would answer equally well. The iodine medication by this method averages 0.7 or 1.5 mg. per day, 0.25 or 0.5 Gm. per year, fifteen to thirty times the safe requirement. In pregnancy, 10 to 20 mg. are given weekly until term; for treatment of simple goiter, 10 mg. daily in alternate months.

The *daily method* aims to give 0.1 to 1 mg. per day, 35 to 350 mg. per year. The lower dosage is doubtless sufficient and absolutely safe; 1 mg. may perhaps become deleterious if it is taken continuously. Since the daily dosage is almost certain to be neglected after a time, it is usually attempted to administer it by some indirect and automatic means, for instance, as "*iodized table salt,*" *i. e.,* salt to which sodium iodide has been added. The Swiss Goiter Commission advises 5 mg. of iodide per Kg. of salt. The average daily consumption of salt in cooking and at table *i. e.,* 10 Gm., would represent 0.04 mg. of iodine. This is quite harmless and quite sufficient, according to Swiss experience (Eggenberger). In the United States, where the iodized salt is less likely to be used exclusively, it is advisable to employ a larger proportion; 100 mg. of NaI per Kg. of salt is now the prevailing American standard (O. P. Kimball, 1937, 1939).

THIOCYANATES (SULFOCYANIDES, SULFOCYANATES, RHODANATES)

The SCN ion reacts similarly to iodide on the aggregation of colloids and in its other effects, antisyphilitic, iodism, and so forth Potassium thiocyanate has been used clinically, especially in hypertension. It is said to lower the blood pressure in the majority of cases, after several days or weeks; but it is so liable to cause untoward results, notably asthenia, that patients must be under careful supervision. Thiocyanates are not dissociated into cyanide, and their acute toxicity is low. On direct contact with frog muscle, thiocyanates cause peculiar contractures. The ion occurs naturally in the body and can generally be demonstrated in normal saliva. It serves to detoxicate cyanide.

Iodide Effects.—The analogy of the colloid effects with those of iodide suggested therapeutic trials with sodium thiocyanate, and it was found to affect neuroses, arteriosclerosis and syphilis in a manner analogous to the iodides (Pauli, 1903 and 1910). It also hastened the elimination of metals, perhaps by rendering the metal-protein compounds more soluble. It resembles the iodides further in producing coryza, acne and other symptoms of iodism. Corper, 1915, observed no results in tuberculosis. Nerking, 1913, reported many disagreeable effects, especially in gastric hyperacidity. A conspicuous difference from iodides is that it does not inhibit *thyroid hyperplasia,* but may provoke it, perhaps by increasing the excretion of iodide.

Bancroft's Theories.—Basing himself on his experience with the dispersive effects of thiocyanate on colloids, and on his assumption that biologic functions, especially those of the central nervous system, are conditioned chiefly on the congelation and peptization of their colloids, Bancroft postulated spectacular effects of thio cyanates on nervous stability, various types of insanity, drug addiction, sciatica, senescence and longevity. These speculations are not supported by sound evidence. Burkholder, 1932, *f. i.*, failed to confirm the antagonism to ether and to morphine as postulated by Bancroft and Rutzler, 1931; Hirschfelder and Cunningham, 1933, also found thiocyanate ineffective against these and against amytal. Schube, 1935, could not confirm Bancroft's classification of psychoses by their response to thiocyanate and amytal.

Efficiency Against Hypertension.—Potassium thiocyanate was reintroduced for this purpose by Westphal, 1924. The continued administration generally leads to persistent lowering of the blood pressure in normal individuals, in three-fifths of patients with glomerular nephritis, and in about a third of hypertension patients. The mechanism of the fall is obscure; the lassitude which it often induces may be a factor. There is practically no fall unless the blood level of thiocyanate is held at 8 to 12 mg. per cent for prolonged periods; improvement is usually seen in two to four weeks, but sometimes not til three months. The *dosage* to maintain this level variel considerably in different individuals, and even in ths same individual, according to renal clearance, fluie balance and other factors. As lower concentrations ard ineffective and higher concentrations are toxic, the levee must be checked chemically (M. H. Barker *et al.*, 1941)l. The *administration* may be started with 0.5 Gm. of potassium thiocyanate daily in water, and adjusted according to the blood level. Rather slight side effects sometimes appear at 15.7 to 21 mg.; but often not with 15 to 33 mg. (L. F. Blaney *et al.*, 1941). Some patients have practically no margin of safety, and serious poisoning has been reported with 13.6 mg. (C. F. Garvin, 1939). The patients must be closely watched and the drug discontinued with the first sign of intolerance. Renal insufficiency and acute inflammations are considered *contraindications.*

In *experimental chronic hypertesnion*, produced in dogs by the Goldblatt method of compressing the renal arteries, oral administration of thiocyanate, 20 to 70 mg. per Kg. daily from one to five weeks, did not significantly lower the blood pressure with the clinical plasma concentrations (8 to 12 mg. per 100 cc.); 15 to 35 mg. levels decreased the pressure in some cases and produced toxic effects in all (D. A. Collins *et al.*, 1940). Goldblatt *et al.*, 1941, also found it ineffective.

Clinical Toxic Symptoms.—A few patients show phenomena analogous to those of iodism: coryza, anginal symptoms, sometimes pustular skin rashes, toxic erythema or papulopustular, even exfoliative, dermatitis (T. W. Baker and Brunsting, 1937). Most patients complain at first of marked fatigue. This wears off in two to six weeks and full vigor returns during treatment, although the blood pressure remains low (Barker, 1935). Many patients feel drowsy even without fall of blood pressure. Vertigo is common, and there are painful cramps and weakness of the arms and legs. Gastro-intestinal disturbances are exceptional at the "safe" level, but nausea and vomiting are among the first signs of toxicity. The flow of gastric juice and its acidity are decreased, as is also the response to histamine (H. W. Davenport, 1940; W. S. Rehm and Enelow, 1934, 1945). Thyroid enlargement with lowered basal metabolic rate occurs occasionally after prolonged administration, and decreases on feeding thyroid (M. P. H. Foulger and Rose, 1943; R. W. Rawson *et al.*, 1943). Ocular disturbances may occur and disappear when the dosage is reduced (J. M Gonzalez and Muñoz, 1944). If the administration is continued, toxic psychosis may develop, similar to bromide mania, with word aphasia and slurring of speech, disorientation, hallucinations, mania and persecution ideas. The symptoms begin at 20 mg. per 100 cc. plasma concentration, and may recede in a week if the drug is promptly withdrawn (Wald, Lindberg and Barker, 1939, review). If the administration is continued after toxic symptoms set in, death may result, even with ordinary doses, and with blood levels not above 21.7 mg. per cent (W. O. Russell and Stahl, 1942).

Toxic Effects on Animals.—As with iodide, the effects tend to develop gradually, beginning with emaciation, diarrhea and (in cats and dogs) vomiting, dehydration, followed in one or two days by hyperexcitability, spastic paresis of the extremities, opisthotonos, convulsions, coma and death. Temperature, respiration, heart rate and blood pressure are not affected directly. With repeated sublethal doses, the hemoglobin decreases. Carbonic anhydrase is inhibited, but the practical significance of this is doubtful (F. J. W. Roughton *et al.*, 1941). Persistent albuminuria with histological renal damage is frequent, even with nonfatal doses. Rabbits often show injury to the gastric mucosa after oral and sometimes perhaps also with parenteral administration. The activity and the toxicity are about the same with all methods of administration, except that intravenous injection produces almost immediate spasticity, which soon relaxes, and is followed by the gradual development of the further effects as with the other methods (Takacs, 1926; Jahr, 1936; Wald *et al.*, 1939). The minimal fatal single dose in rabbits is 0.5 Gm. per Kg., hypodermically (or intravenously, Corper, 1915). The effects are specific and not merely "salt actions," for they were absent with sodium chloride in double the dosage (Jahr). F. Franz, 1912, confirmed that no cyanide is split off in the animal organism. Even 0.36 Gm. per Kg. produces practically no acute effect on the circulation, respiration or bile and urine flow (Gies, Lieb and Kahn, 1914). Exposure of *amphibian larvae* to thiocyanate results in hyperdevelopment of various parts of the central nervous system (S. Ranze, 1945). The pharmacology of *organic thiocyanates* was studied by Taubmann, 1930, their toxicity by von Oettingen *et al.*, 1936. They are used as *insecticides* (fly sprays), especially butyl carbitol thiocyanate (D. F. Murphy, 1936). They act on the isolated heart of the cockroach (J. F. Yeager *et al.*, 1935).

Skeletal Muscle.—Immersion of a frog's gastrocnemius in a 2 per cent solution of sodium thiocyanate (in Ringer's solution) produces a strong primary contraction, followed by gradual increase of tonus, slow waves of contraction and intermittent twitchings (Worthington, 1912; Langley, 1916). The action appears analogous to that of monoiodoacetate. The twitchings and their synergisms and antagonisms were studied by Okagawa, 1926. At first they are arrested by curare; *i. e.*, they are of nervous origin. As the concentration in the muscle rises, however, the muscle substance is also involved, so that curare becomes ineffective (Langley, 1916). G. E. Selter, 1927, confirmed that the thiocyanate increases the lactic acid formation.

The fate of thiocyanate in the body is like that of the haloids. It is *excreted* chiefly by the urine, similarly to iodide, but more slowly and less completely, so that there is a tendency to cumulation, especially in glomerular nephritis. The urinary clearance varies rather widely and does not parallel urea clearance. In man, with a single dose of 0.3 to 1 Gm., the excretion continued more than three weeks, and only 10 to 50 per cent was recovered. Rabbits excrete it more efficiently (Baumann, Metzger and Sprinson, 1934; Goldring and Chasis; Barker, 1935; Wald *et al.*, 1939).

The *distribution* of administered thiocyanate, like that of the haloid anions, is practically exclusively in the extracellular fluid, so that it may be used as a measure of the latter; the result is somewhat too high, as it passes into the cells more readily than does chloride (J. R. Elkinton *et al.*, 1943). Its concentration in the serum, lymph, urine, gastric juice and saliva is nearly equal, three hours after intravenous injection into dogs (Crandall, 1932). The concentration in the *cerebrospinal fluid* is the same as in the serum or slightly lower, never higher (R. Blum, 1928; Wallace and Brodie, 1940). It diffuses readily into the *synovial fluid*, attaining a concentration about 9 per cent below that of the serum. It passes fairly rapidly into the *aqueous humor, reaching* a maximum ninety minutes after intravenous injection in rabbits, but its concentration is much lower than the blood level (P. H. Lavities *et al.*, 1936). The passage is favored by physostigmine and pilocarpine, rather hindered by atropine; the effect of epinephrine is doubtful (Kudo, 1931). The *salivary excretion*, in rabbits, occurs chiefly through the epithelium of the excretory ducts (Scholari, 1928).

Normal Occurrence.—Small quantities of thiocyanate are formed from the cyanide which arises in the metabolism of protein, or which may be introduced in tobacco smoke or with vegetables such as succotash and onions. It is found in the blood and all body fluids, in fairly equal concentration, about 0.03 to 0.06 mg. per 100 cc., and is excreted by the urine and feces, generally in the ratio of about 1:2. The total excretion in man is of the order of 3 or 4 mg. per day. Its quantity is increased by tobacco smoke (A. Trasoff and Schneeberg, 1944) and decreased by catharsis (indicating that either CN or SCN is formed in the alimentary canal; E. J. Baumann *et al.*, 1934). Experimentally, it is increased by administering cyanides or nitriles and by feeding amino acids (alanin) or by increasing the protein intake, but not by sulfur, sulfide, thiourea or taurine (Kahn, 1912, bibliography; Gies, Lieb and Kahn, 1914; Obreggia *et al.*, 1933; Stuber and Lang, 1933). Some proteins with loosely combined sulfur convert KCN into KSCN at room temperature *in vitro* (Pascheles). Thiocyanate is formed slowly from cyanide by methylene blue *in vitro* (R. G. Smith, 1940).

The *occurrence* of thiocyanate in *human saliva* has aroused especial clinical interest. Thiocyanate is found in the human parotid and submaxillary saliva, but not in all individuals; also in the saliva of many animals, but not in dogs and horses. It reflects generally the plasma level and is therefore increased by smoking. It is absent in newborn infants (Rittershain); also in suppurative middle-ear disease (Juergens, 1901). It has no relation to tooth decay (Lothrop and Gies, 1911): The quantities present in the mouth could not have an antiseptic effect (Gies and Kahn, 1912 and 1913); although thiocyanate is toxic to higher plants, and in greater concentrations also to bacteria. Sulfocyanic acid (0.3 to 0.4 per cent) inhibits the gastric digestion of fibrin (Cavazzani, 1915).

NITRATES

Nitrates resemble the haloid salts, especially iodide, in physicochemical properties, and also in their effects, although these may be complicated by reduction to nitrite. They were formally employed for diuresis, to depress the circulation in fevers, as anaphrodisiacs and for a variety of other conditions, but are now rarely administered. Saltpeter, KNO_3, and Chile saltpeter, $NaNO_3$, are used as antispetic to pickle "corned" meat and to cause its red color by reduction to nitrite, which converts the myohemoglobin to methemoglobin. No harm results from this as customarily used; but if the meat is not washed, it may produce symptoms. Serious poisoning may result from overdosage of the salts, which have a varying toxicity.

Clinical Uses.—Potassium nitrate was used extensively in the eighteenth century, before iodide was discovered. The indications were as numerous and vague as the claims for iodide. Allston at that time (quoted by Stillé) described it as resolvent, antiseptic, antiphlogistic, diuretic, purgative and anaphrodisiac. It was used extensively against *rheumatism* in England between 1750 and 1800; as niter paper it was used against *asthma* in 1842. It was tried against *scurvy*, but quickly found useless. It continued to be used against *sore throat* (Brunton), somewhat like potassium chlorate. Its use as *anaphrodisiac*, which is still popular, is but little discussed in medical writings. Stillé, 1874, refers it to Allston and to Boerhaave. There is no scientific evidence of such action, but if it exists it might be a part of the general apathy which its continued use may induce, analogous to thiocyanate. The *diuretic effect* was described in the seventeenth century. Some observers reported it as striking, others as slight and uncertain. Stillé points out that the water intake was not well controlled. Norman Keith, 1931, found ammonium nitrate, up to 10 Gm. per day, effective in man and dogs, to reinforce mercurial diuresis. This salt acidifies the urine as does ammonium chloride, so that the effect is mixed. The large dosage appears to be necessary and may give rise to serious toxic effects.

Serious and fatal acute poisoning has occurred through mistake for Epsom salts. The symptoms consist in great abdominal pain, vertigo, muscular weakness, vomiting, frequently bloody stools; irregular pulse; convulsions and collapse; tenesmus and suppression of or albuminous and often bloody, urine. The heart and respiration are not greatly damaged. The gastro-enteritis may be so violent as to lead to an early fatal ending, in twenty minutes to five hours. Lewin states the clinical fatality as 56 per cent. The *autopsy* generally shows gastritis and enteritis, with hemorrhages into the submucous coat and sometimes into the lumen. Ulceration and corrosion of the mucosa has been observed (Lewin). The *treatment* consists in dilution. Large quantities of water should be swallowed and the stomach washed. Demulcents, milk, egg white, acacia, are also useful. The symptoms should be met as they arise.

Therapeutic and *Toxic Dosage.*—Stillé states the therapeutic dose as 5 to 15 grains every one to three hours to a total of 60 to 180 grains (4 to 12 Gms.), but poisoning may result if the daily dose exceeds 4 Gm., or if the single dose is more than 1 Gm.; 5 Gm. at one dose may be dangerous; 8 Gm. may be fatal, and 15 to 30 Gm. are generally fatal; but 30 and even 60 Gm. per day have been taken for two months without marked disturbance (Stillé). The toxicity is greater if the amount is taken at one time and in concentrated form; but there appear to be other unknown reasons for the variable toxicity. The mechanism of the local violent irritation is also obscure. It occurs also on contact of other mucosae and of wounds with solutions that are not too dilute. Ammonium nitrate produces pruritus and other cutaneous irritation in munition workers. Nitrates provoke the *luetin reaction* (Cole and Paryzek, 1917). *Excised ureter* is slightly stimulated by nontoxic concentrations (Macht, 1917).

Minor toxic actions from continued therapeutic doses resemble those of thiocyanate, bromide and iodide: general weakness and lassitude, physical and mental, low spirits, drowsiness; giddiness, headache, confusion; debility of the arms or legs lasting for a week, and so great that patients believe themselves paralyzed; speech and memory defects, general trembling; pulse weak and slowed, sometimes 20 per minute, the effect persisting for a week after discontinuing the drug. The appetite and dizziness may be normal; there may be bloody diarrhea (Löffler, 1849; Jörg; Cargill, 1851). Fackelmann, 1898, reported hemorrhagic tendencies, edema and fatty heart.

Fate and Excretion.—Nitrates are readily absorbed. Their excretion is similar to that of the halogen ions, and shows the usual mutual relation (Sollmann). Practically the entire quantity is excreted unchanged (Abderhalden and Hirsch, 1913), but a small proportion may be reduced to nitrites. This reduction takes place so slowly, in the inorganic nitrates, that no nitrite action can ordinarily be seen; but large doses may cause methemoglobin formation (Binz and Gerlinger, 1901). Metabolism studies have given contradictory results (Grafe and Wintz, 1913). After giving large doses of ammonium nitrate to dogs, Whalen, 1935, found about 50 per cent excreted by the urine; the remainder was probably destroyed in the tissues.

Normal urine contains 0.1 to 0.4 per cent of KNO_3. This is considerably more than is ingested with the food, so that a part must be formed as an end product of metabolism (H. H. Mitchell, Shonley and Grindley, 1916).

Potassium Nitrate, U.S.P. (Niter, Saltpeter): KNO_3; and *Sodium Nitrate* (Chile Saltpeter) are freely soluble in water. They have a saline cooling taste. Dose, 0.3 to 1 Gm., 5 to 15 grains, diluted.

POTASSIUM CHLORATE

The saturated (1:16) solution is used as mouth wash in stomatitis, especially the ulcerative (Vincent's angina), where it was supposed to be specific; and as a prophylactic against mercurial stomatitis, in which a similar collaboration of putrefactive microorganisms is concerned. It is also employed as a gargle in pharyngitis and tonsillitis. It often seems to be effective, but its action is unexplained. It was introduced with the idea that it would act as an oxidizer, and thus be antiseptic. However, it does not easily part with its oxygen in the body, being excreted practically unchanged. Its efficacy is questionable, except that the tablets, when dissolved slowly in the mouth, at least change the inflamed taste to the cool and clean saline taste of the potassium chlorate. After a few days of the ordinary use of the tablets, the potassium taste continues from the blood. Patients should be cautioned against swallowing the tablets or gargle, as this has repeatedly led to serious toxic effects (A. Jacobi, 1879), especially by the production of methemoglobin and destruction of the corpuscles, thrombosis, and so forth.

Potassium chlorate is used as tablets of 0.25 Gm., 4 grains, dissolved slowly on the tongue two to five times daily; or as a mouth wash or gargle of the saturated (1:15) aqueous solution; often with ferric chloride, which liberates some chlorine when it is added without dilution.

Potassium chlorate poisoning is fairly common, either by an overdose, since the laity does not generally regard it as a toxic substance, or in the therapeutic use, as the susceptibility varies greatly, which is likely to lead to carelessness. In general, 10 Gm. may be considered as toxic, 15 to 30 Gm. as fatal (Lewin). The mortality is about 70 per cent. The symptoms may start at once or be delayed to six hours; death may occur in six hours to seven days.

The *symptoms of poisoning* are gastritis (nausea, vomiting, gastralgia); methemoglobinemia (cyanosis, collapse and terminal convulsions); and nephritis (lumbar pain, anuria, albumin, casts, blood, and so on). The postmortem findings correspond with the symptoms.

Treatment consists in gastric lavage, hot drinks and symptomatic measures. Intravenous injection of physiologic saline solutions should hasten elimination of the chlorate.

Continued administration of doses which do not cause methemoglobin production lead to emaciation, probably a haloid effect (A. P. Richardson, 1937).

Blood Changes.—When the chlorates are added to blood, either inside or outside the body, they effect the *formation of methemoglobin.* The chlorate ion is not used up in this process, so that it may convert an indefinite amount of hemoglobin. They differ in this respect from the nitrites (see Index), and their action is in consequence more violent and more prolonged. They may produce actual asphyxia. In a severe case of human poisoning the blood, examined thirteen hours after taking the chlorate, contained both methemoglobin and hematin. Hemolytic icterus developed later. Similar conditions were found in poisoned animals (Feigl, 1916). In addition to this formation of methemoglobin, the chlorates break up the *blood corpuscles* (Huber, 1912). This may produce embolism; the proteins, and so forth, which are liberated by the destruction of the corpuscles are irritant to the kidneys and produce interstitial *nephritis*, with the usual phenomena—proteins in the urine, casts, sometimes hemoglobin compounds. Possibly the chlorate ion itself irritates the kidneys. *Fat embolism* of the lungs and other organs occurs at least in animals, from the bone marrow. The blood contains numerous normoblasts. Fragmentation of the heart muscle is a frequent cause of death (Winogradow, 1907).

Methemoglobin Formation by Chlorates.—The blood of different animals shows different degrees of susceptibility to the methemoglobin formation. These differences are common with all poisons acting on the blood, especially as between carnivorous and herbivorous animals. The cause is not understood, but is perhaps connected with differences in the alkalinity of the body. The conversion occurs fairly readily *intra vitam* in man, dog and cat, while rabbits and guinea pigs are almost immune. But in the test tube, chlorates convert rabbit's blood, although more slowly than dog's. The action is much slower outside the body, often requiring several hours. The concentrations injurious for the blood were determined by E. Caesar, 1918.

Iodates and bromates have a similar action on hemoglobin (Heinz, 1898).

Excretion.—Chlorates are excreted mainly by the urine, but partly also by the saliva. The urinary excretion begins promptly and is completed within forty-eight hours, about 90 per cent of the chlorate being recovered (Rosenbloom). A great deal of this is reduced to chloride after the urine is voided. It is doubtful whether this reduction occurs ordinarily in the body. *Bromates* are partly reduced in the tissues, and *iodates* intensively when given by mouth, but not when administered hypodermically or by vein (Crespolani, 1909).

The **distribution** of fatal doses was studied by Rosenbloom, 1912.

***Potassium Chlorate,** $KClO_3$, occurs as colorless crystals or white granular powder; odorless; cooling, characteristic taste. Sol. in water (1:16.5); nearly insol. in alc.; sol. in glyc. *Explosive* when triturated with organic matter (not when in watery solution), or with charcoal, sulfur, sulfides, hypophosphites, reduced iron, and so on. Dose, 0.3 to 0.6 Gm., 5 to 10 grains.

Perchlorate was studied on the isolated frog heart by Cartolari, 1930.

Bromates act similarly to chlorates, but are considerably more toxic, mainly by central paralysis (Santesson and Wickberg, 1913). They form methemoglobin *in vitro*, but not so actively as chlorates (Mehring, 1885; Cushny, 1908).

Iodates.—Macciotta, 1916, found KIO_3 to be tolerated without disturbance, with oral administration of 0.285 Gm. per Kg. The urine contained no trace of iodate, but only iodide. Hypodermically, the above dose was fatal.

Intravenous injection (5 cc. of 2 per cent) into rabbits produces pigmentary changes in the retina, without other damage (A. Sorsby, 1941).

THIOURACIL, THIOUREA, AND RELATED ANTITHYROID SUBSTANCES

These inhibit the formation of thyroid hormone by the thyroid gland. The action of thyroxin itself, for instance on the basal metabolic rate, is not diminished. Several days or weeks are therefore needed for the full development of the effects, especially if the patient has received iodine. The deficiency of thyroxin production stimulates the production of thyrotropic hormone, which produces ineffective hyperplasia of the thyroid epithelium. This does not occur if thyroid is fed or if the hypophysis is excised. The decreased production of thyroxin is used to suppress hyperthyroidism, and expecially to prepare patients for operation. The effect lasts only during the administration; but if the administration is continued for an average of ten months, 60 to 80 per cent of the patients retain more or less benefit (Beierwaltes and Sturgis, 1946). Thiouracil is more effective than iodide, but acts more slowly, the basal metabolic rate returning to normal in three to six weeks. It usually causes little or no side effects, but adverse reactions, including serious granulopenia, occur in a considerable proportion of patients. It is therefore recommended only for preoperative treatment, not for permanent therapy, unless surgical intervention is especially contraindicated. The patients should receive detailed warning as to untoward symptoms and instructions to report these immediately.

Historical.—The discovery of these antithyroid actions started with the observation of J. B. Mackenzie *et al.*, 1941, that sulfanilyl guanidine induced thyroid hyperplasia in rats, which was not influenced by iodide administration, but was arrested by thyroxin. The structural similarity of the sulfonamide group, $H_2N\text{-}C_6H_4\text{-}SO_2NH_2$ to thiourea, $H_2N\text{-}CS\text{-}NH_2$, suggested that the latter would also have this action. This was confirmed by C. G. MacKenzie and MacKenzie, 1943. E. B. Astwood, 1943, showed that it is produced by most thiourea derivatives; thiouracil, $\underbrace{NH\text{-}CS\text{-}NH.COCHCH}$, was found to be especially suitable. The comparative antithyroid actiln of thiourea and allied substances was studied by R. H. Williams and Frame, 1945. The action is also produced by para-aminobenzoic acid, $NH_2\text{-}C_6H_4\text{-}CO_2H$, and by thiobarbituric acid.

Morphologic Changes.—C. G. MacKenzie and MacKenzie, 1942, showed that administration of sulfonamides and thiourea to mice and dogs results in hyperemia and marked enlargement of the thyroid, with reduction of the colloid and increased height of the cells. Guinea pigs and chickens did not appear to respond; but J. P. Mixner *et al.*, 1944, confirmed thyroid enlargement in chickens by appropriate dosage. E. B. Astwood, Sullivan *et al.*, 1943, showed that the hyperplasia is not influenced by giving iodine, but that it is suppressed by giving thyroid or by excising the hypophysis. *Continued administration of thiouracil from birth induces cretinism* in rats (A. M. Hughes, 1944). *Excessive administration* to human subjects also results in lowering of basal metabolic rate, myxedema, and increased blood cholesterol (E. Shorr, 1944).

R. Grasso, 1946, attributes the changes in the thyroid cells to *excessive secretion of anterior pituitary thyrotropic hormone.*

Thyroid Iodine.—Thiourea administration rapidly decreases the iodine content of both the thyroxin and non-thyroxin fractions of the thyroid gland, the iodine being rapidly excreted by the urine (E. J. Baumann *et al.*, 1944). When 0.1 per cent of thiouracil is added to the drinking water of rats, the loss of thyroid iodine begins within a day and continues for five days, when a stable level of about a thirteenth of the normal is reached. When the administration ceases, the accumulation of iodine in the thyroid begins within a day and reaches nearly normal in seven days. Addition of iodine to the diet has little effect in the loss or reaccumulation. Similar effects are produced by *sulfadiazine* (Bissell and Astwood, 1944), but it is less potent. Thiourea thyroids accumulate little radioactive iodine when this is administered (A. S. Keston *et al.*, 1944). *In vitro conversion of inorganic iodine into diiodotyrosine and thyroxin* by slices of thyroid gland is inhibited by thiourea, thiouracil, para-aminobenzoic acid, thiocyanate and sodium cyanide (A. L. Franklin *et al.*, 1944). The action is therefore directly on the cells, and the cyanide effect indicates some *enzymatic interference*, as had been surmised by Astwood. Administration of thiouracil to rats inhibits the *cytochrome oxidase* of their thyroid, without interfering with that of bone marrow, kidneys, and other tissues (K. E. Paschkis *et al.*, 1945).

Corollary Effects of Thyroid Inhibition.—Thiouracil is reported to be effective for decreasing or suppressing the clinical symptoms of *angina pectoris*, in a majority of patients, similarly to thyroidectomy, presumably by diminishing the epinephrine sensitivity of the cardiovascular system. This may begin with 0.4 Gm. daily in divided doses, and continue with 0.1 Gm. Improvement begins in one and a half to five weeks (W. Raab, 1945).

Resistance to anoxia from reduced atmospheric pressure or carbon monoxide is increased by pretreatment of rats with thiouracil (A. M. Hughes and Astwood, 1944) or thiourea (A. S. Gordon *et al.*, 1944), presumably by the lowered oxygen requirements. Thiourea retards *tadpole* metamorphosis (A. S. Gordon *et al.*, 1943), and inhibits the growth and development of secondary sex characteristics of certain fish (E. D. Goldsmith *et al.*, 1944).

Thiouracil decreases the *lactogenic* hormone in the anterior pituitary. This is imperfectly antagonized by estrogenic hormone (J. Meiter and Turner, 1947).

Hyperthyroid patients are almost uniformly improved by the administration of thiouracil or other thiourea derivatives. These are ineffective against similar symptoms if these are not due to hyperthyroidism; nor are these drugs of any value against simple goiter. In toxic goiter, they produce gradual but complete remission of all the toxic symptoms. They lower the basal metabolic rate, allay the nervous irritability, increase body weight, restore the normal Ca, P, N, creatine, and cholesterol metabolism, similarly to iodine administration or thyroidectomy, but more slowly. The exophthalmos is also usually improved. Thyrotoxic patients who have received thiouracil for five or six weeks prior to surgical procedures react to these like normal individuals. The remission is more complete and more stable than with iodide, but requires more time, and the vascularity of the gland is increased. The probability of toxic reactions weighs seriously against it (review, E. B. Astwood, 1944; H. M. Clute and Williams, 1944; R. W. Rawson and McArthur, 1946; Aranow, Elliott *et al.*, 1946). If the administration is stopped without operation, the toxic state returns within one or two weeks; but if this is maintained for longer than six months, remission may sometimes endure, but this is exceptional. The risks of toxic reactions, however, are probably greater than for those of thyroidectomy.

Toxic effects of thiouracil, granulopenia, leukopenia, drug fever, or dermatitis occurred in about an eighth of the 5745 patients' records which were surveyed by W. Van Winkle *et al.*, 1946. Some complained of nausea, dizziness, headache or abdominal cramps. In a similar series, F. D. Moore *et al.*, 1946, report that about 10 per cent of patients have reactions which indicate that administration should be stopped. Death attributable directly to the drug amounted to about 0.5 per cent. Most of the observers believe that the incidence of adverse reactions is probably less than with other treatment methods, but the patients must be carefully watched. Mild and juvenile cases of hyperthyroidism can usually be treated successfully by other means, with less risk.

Granulopenia, the most serious complication, occurred in 2.5 per cent of the patients (1.8 per cent, Moore), and proved fatal in about 0.4 per cent of these cases. It is unpredictable, has no relation to dosage, and is most frequent in the first four weeks of administration. This should be discontinued with the first sign of sore throat, coryza, fever, malaise, and change of blood count. The most effective treatment is by parenteral penicillin, 500,000 units daily. E. H. Fishberg and Vorzimmer, 1945, recommend pyridoxine, 0.2 Gm. daily, for protection, 0.2 to 0.5 Gm. daily by vein for treatment. *Leukopenia* with a cell count of less than 4000 occurred in 4.4 per cent, also without relation to dosage. It may improve with continued administration, but it may also be an early indication of granulopenia. *Drug fever* occurred in 2.7 per cent (5 per cent, Moore), generally during the first week. Various *skin reactions* occurred in 3.3 per cent, also without relation to dosage. They were usually mild (W. Van Winkle *et al.*, 1946).

The *granulopenia* is attributed to destruction of the cells of the bone marrow in the promyelocyte stage (Gargill and Lesses, 1945). These observers also report occasional *jaundice*, and swelling of the submaxillary gland.

Long-continued administration of thiouracil (feeding 40 mg. daily for three to four months to rats) produces *marked changes in other viscera;* particularly extreme congestion and involution of the *adrenal cortex,* involving all three zones; progressive hypertrophy of the adrenal medulla with increase of epinephrine content; shrinkage of the spleen pulp; parenchymatous degeneration of the liver; atresia of the gonadal follicles, and depression of spermatogenesis; deposits of thiouracil in the kidneys and urinary tract (E. J. Baumann and Marine, 1944). Thiouracil neutropenia has been produced in rhesus monkeys (Aranow, Engle and Sperry, 1946). Addition of 0.1 per cent of thiouracil prevented the occurrence of cirrhosis by special synthetic diet (P. György and Goldblatt, 1945).

Fate.—Thiouracil is rapidly absorbed from the gastrointestinal tract, but about 15 per cent is destroyed before absorption. It is distributed through all tissues and fluid; the blood corpuscles contain more than the plasma. Considerable is destroyed by many tissues. A third to two-thirds of the clinical dosage is promptly excreted by the urine (R. H. Williams *et al.*, 1944). More constant serum levels are obtained if it is administered at frequent intervals than with a single daily dose (K. E. Paschkis *et al.*, 1945).

Administration of Thiouracil.—The full therapeutic effect is usually obtained with 0.1 Gm. four times daily, in water, continued for four to eight weeks, until the symptoms improve sufficiently. The response is delayed if iodine has been administered or if the glands are large and soft. The remission may last twenty weeks (W. Van Winkle *et al.*, 1946). If the treatment is to be continued instead of operation, the maintenance dosage should be reduced to 0.1 Gm. twice daily, and after three months to once daily (R. H. Williams and Clute, 1945).

Thiouracil, N.N.R., a white powder of bitter taste, very soluble in water, slightly soluble in alcohol. Marketed as tablets of 0.1 Gm. *Patients should be given written instructions* to report immediately any symptoms of sore throat, fever, coryza or malaise.

Other antithyroid agents of this group which have received clinical trial against hyperthyroidism include 6-propylthiouracil, 4-methylthiouracil, aminothiazole, thiourea, thiobarbital, and para-aminobenzoic acid.

Propylthiouracil.—Astwood and Vander Loan, 1946, who assayed some 300 thiouracil derivatives, found the antithyroid potency of 6-n-propylthiouracil and 6-ethylthiouracil about ten times greater than that of thiouracil in rats, about five times in man. Its toxicity is also greater, but not proportionately, and it is therefore better tolerated. The clinically effective dose varies; 50 to 150 mg. daily are required to restore metabolic equilibrium. Ordinarily, 50 mg. every eight hours is advised for severe cases, every twelve hours for milder ones. The effective dose should not be decreased until all manifestations of the disease are controlled. W. S. Reveno, 1947, considers its therapeutic potency as three times that of thiouracil, the dosage therefore as a third. It is much less likely to produce toxic reactions, but may occasionally do so.

Methylthiouracil is reported by A. Wilson, 1946, to produce a more rapid response than thiouracil in thyrotoxicosis, with less toxic effects. Smaller doses suffice for maintenance.

Aminothiazole ("Abadol") has been used in France. Four tablets of 0.1 Gm. daily for three to four weeks markedly improve thyroid toxicosis. No untoward effects have been reported (J.A.M.A., 1945, 129:761; M. Perrault and Bovet, 1946).

Thiobarbital is about twice as potent as thiouracil on patients (Astwood, 1945), and with moderate doses on rats (E. B. Astwood, Bissel and Hughes, 1945). The clinical thyrotoxic manifestations are successfully controlled by 0.1 to 0.4 Gm. daily, but there is a high incidence of complications, including granulopenia and acute liver disorder.

Para-Aminobenzoic Acid ("PABA") has been used in human thyrotoxicosis as the sodium salt, up to 1.5 Gm. daily and up to nine months. It appears to be slower, but equally effective as thiouracil and is less toxic. Patients remained well four to fifteen months after discontinuing the administration (L. Berman, 1945).

"*Promizole*" is the most active of the sulfone goitrogenic agents, but its potency is only a fifth of thiouracil. Sulfides are more potent than sulfones (D. A. McGinty and Bywater, 1945).

Thiourea (Thiocarbamide), 1 to 2 Gm. daily, is as effective as thiouracil against thyrotoxicosis, and has a similar toxicity (C. R. St. Johnson, 1944). It is not used, as it gives a characteristic odor to the breath and its taste is disagreeable (E. B. Astwood, 1943).

The toxicity of thiourea for animals is usually low (also that of *thiuramdisulfides;* Hanzlik and Irvine, 1921). Rats consumed for more than three years 25.5 mg. per Kg. of body weight daily (less than is usually required to produce marked thyroid hyperplasia) without any significant effects on growth, mortality or pathologic changes attributable to the thiourea (A. Hartzell, 1945). Antithyroid doses interfere with reproduction, but this returns to normal when administration is stopped. If it is fed to lactating mothers it is excreted by the milk so as to produce thyroid hyperplasia and retarded growth in the young (E. D. Goldsmith *et al.*, 1945). In adult rats, thiourea may produce neutrophilic *granulopenia,* which may be prevented by the simultaneous administration of liver (E. D. Goldsmith *et al.*, 1944). The *acute toxic phenomena* are chiefly pulmonary congestion and edema (J. B. MacKenzie and MacKenzie, 1943). The toxicity is greatly increased by thyroid feeding, and decreased by thyroidectomy. Adrenalectomy does not increase the incidence (D. Marine and Bauman, 1945). Potassium iodide protects against the acute thiourea toxicity; the chloride and bromide do not. The toxicity and the protection are not related to the thyroid effect (W. E. Griesbach *et al.*, 1944). The thiourea hyperplasia disposes rats to the production of *thyroid cancer* by 2-acetoaminofluorene (F. Bielschowsky, 1944). Thiourea is an effective *antioxidant.* It may be used as stabilizer in solutions of ascorbic acid (W. R. Fearon, 1942), epinephrine, metycaine, and so forth. Dipping sliced apples in 0.1 per cent thiourea solution prevents their browning. Thiourea inhibits the growth of gram-negative bacteria (L. Weinstein, 1946).

Like thiouracil, thiourea produces fatal lesions of the suprarenal cortex in rats (G. E. Glock, 1945).

Fate.—Thiourea is rapidly absorbed, widely distributed, and promptly excreted by the urine. The urine clearance is close to urea. About 25 per cent is recoverable from the urine after administration of 1 Gm. to man. The remainder is for the most part broken down; none is excreted in the feces. The concentration in the milk approaches that of the serum (L. C. Chesley, 1944; R. H. Williams and Kay, 1945). Patients receiving up to 2 Gm. orally have blood levels of less than 5 mg. per 100 cc. (D. Campbell *et al.*, 1944). When injected into dogs, it appears to be distributed in concentration corresponding to the total volume of body water, rather than of extracellular water, so that it must enter cells freely (T. S. Danowski, 1944).

Thiourea Derivatives as Rat Poisons.—The pulmonary edema which was mentioned under thiourea is also produced by a number of its derivatives, rendering them acutely fatal, especially to certain strains of the Norway rat. This was noted accidentally with *phenylthiourea* by C. P. Richter, 1945, who investigated a large series of these compounds and found "ANTU" especially practical for community rat extermination.

Alpha-naphthyl-thiourea (ANTU) compares favorably with other rat poisons in cost, toxicity, and voluntary acceptance by rats. It is considerably more toxic to Norway rats than to other animals, killing them by pulmonary edema and pleural effusion. Dogs are fairly susceptible, but are generally protected by vomiting. No human fatalities occurred in three years of extensive use in Baltimore. Treatment would be by liberal gastric lavage, the substance being very little soluble. No antidotes are known (review, F. S. Philips, 1946).

The LD_{50} for Norway rats by stomach tube is 7 mg. per Kg. of body weight. Mice and dogs rank next in susceptibility; Alexandrine rats, squirrels, and so forth, are much more resistant. The cause of these differences is not known.

The action is presumably on some enzyme system. It involves greatly increased lymph flow from the lungs and heart. The heart muscle and the lung capillaries do not appear to be affected. The temperature is lowered. Nonlethal doses stop hair growth and skin pigment production. These resume when the administration is stopped (C. P. Richter, 1945). There is marked increase of *blood sugar,* to nearly three times the normal level in two and a half hours, with severe fall of liver glycogen, and failure to deposit liver glycogen. Cysteine affords considerable protection against the toxicity (K. P. DuBois *et al.*, 1946). Adult Norway rats show acute toxic effects when 100 ppm are added to the diet, and 0.1 per cent is uniformly fatal. Intermediate doses, to 800 ppm, develop a high degree of tolerance, sometimes to fifty times the ordinary fatal dose, owing partly to refusal to eat freely. The tolerance decreases in a few weeks if the drug is withheld (C. P. Richter, 1946; F. S. Philips, 1946).

Chronic poisoning, secured by 50 to 800 ppm continued up to two years, produces stunted growth, "spectacle eyes," thinning and coarsening of hair, deformities of the legs and feet, hyperplasia of the thyroid and splenic pulp, hyaline changes in the hepatic cells, decreased thickness of adrenal cortex, and calcified tubular casts (O. G. Fitzhugh and Nelson, 1947).

With *dogs,* death occurs by pulmonary edema with pleural effusions, attributed to damaged capillaries. The effusions show increased albumin: globulin ratio. Feeding gradually increases the tolerance (A. Chanutin *et al.*, 1947). Continued administration to *cats* produces fatal intrahepatic obstructive jaundice, without pulmonary lesions.

Phenylthiocarbamide generally kills rats by pulmonary edema, two to eighteen hours after administration of 1 mg. Repeated administration develops considerable tolerance. Thyroid hyperplasia ensues (C. P. Richter and Clisby, 1942).

Dithiobiuret, when administered orally for several days, produces progressive paralysis of skeletal motor function in rats. This may be maintained for weeks by adjusting the dosage, and recovery occurs promptly if the administration is discontinued. A single hypodermic injection does not produce the paralysis even with a dose twenty times as great as the total cumulative oral dosage. The muscle and nerve of the paralyzed animals respond normally to direct stimulation; the acetylcholine and cholinesterase content are normal; the paralysis is not relieved by neostigmine. The action must therefore be central (E. B. Astwood, Hughes *et al.*, 1945).

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THE REACTION OF THE BODY (REMOTE EFFECTS OF ACIDS AND ALKALIS)

The $H(^+)$ ions of acids and $OH(^-)$ ions of bases part readily with their electric charges, and therefore alter the state of colloids. In this way, and also by direct chemical changes, they produce extensive alterations in the functions of cells, which would be rapidly fatal if they exceeded a certain degree. These effects are produced only by the dissociated ions, which represent the *actual* acidity and alkalinity. The activity of an acid or base depends therefore not only on its total concentration, but also on its dissociation. The mineral acids, which dissociate freely, are much "stronger" than equimolecular solutions of the organic acids or acid salts, which dissociate only slightly. Undissociated molecules do not exert these actions, but neutralize added acid or alkali, in proportion as the free ions become combined, and in *this* respect are equivalent to the dissociated ions. They may be considered as *potential* acidity or alkalinity.

(Conçepts of *p*H are reviewed by A. G. Ogden, 1947.)

The *normal reaction* of the living tissues and fluids within the body proper is near neutrality, that of the fluids inclining a trifle to alkalinity (*p*H = 7.1 to 7.8, generally 7.35 to 7.43). The digestive juices and urine are the only fluids in higher animals which normally depart from this rule. The neutrality of the blood is maintained even in acidosis; although the cells where the pathologic acid is formed presumably develop increased acidity. Normal living cells have an alkaline, neutral or slightly acid reaction, judging by *intra vitam* stains.

Regulating Mechanisms.—Metabolism leads to the production of acids (carbonic, lactic, sulfuric, phosphoric, and so on) which would tend to increase the acidity of the body. The carbonates derived from the combustion of vegetable salts would tend to render it alkaline. The maintenance of the normal, nearly neutral reaction is regulated with great nicety, however, by the use of several mechanisms. The carbonates and alkaline phosphates of the blood and tissues constitute a stock of potential alkali, and the carbonic acid and acid phosphates of potential acid. These are sufficient to "buffer" at once all ordinary attempts to change the actual reaction. The amphoteric character of the proteins permits them to neutralize a limited quantity of either acid or alkali. The administration of acid or alkali by mouth therefore does not change the *actual* reaction of the blood and tissues, but only the *potential* acidity or alkalinity, *i. e.*, the *alkali reserve.* The final restoration of the total acid-base equilibrium is accomplished by the excretion of CO_2 by the lungs, of acid or base by the urine, and by the adjustment of the ammonium-urea metabolism.

Reaction of Normal Blood.—The *p*H of fresh defibrinated blood is weakly alkaline, almost neutral, 7.45 for arterial, 7.3 for venous (Hasselbach, 1913); 7.6 to 7.8 for human serum, 7.4 to 7.6 for oxalated blood (Levy, Rowntree and Marriott, 1915), at air temperature; at 37° C. the alkalinity would be about 0.1 higher. In normal animals, feeding with acids or alkalis has practically no effect on the H concentration of the blood. Even when symptoms of acidosis are present, the alkalinity is but little decreased (*p*H of serum, 7.2 to 7.5; Levy *et al.*). Under alkali therapy, this is restored toward normal. Intravenous injection of acid into dogs or rabbits produces death when *p*H 6.9 is reached (Levy *et al.*). Concentrations above *p*H 8 are probably also fatal (Rowntree).

Buffering Mechanisms of the Blood.—It is relatively difficult to alter the reaction of blood even *in vitro.* Friedenthal, 1903, showed that serum requires, to secure a given change of reaction, thirty to forty times as much NaOH, and three hundred twenty-seven times as much HCl, as would be needed in water. This stability is due to the presence of the salts of weakly dissociating acids, which limit the liberation of $H(^+)$ ions to practical neutrality. This property is especially marked with phosphates and carbonates, which are important "buffer" constituents of the serum. The proteins act similarly. The chief alkaline buffer of the serum is the bicarbonate. *In whole blood*, the corpuscles play an important part in buffering, not inferior to that of the plasma, both in carrying and in releasing CO_2, their hemoglobin acting as a weak, polybasic acid which binds alkali, but releases it readily to carbonic acid. This function is enhanced by the special permeability of the corpuscles, which permits the passage of CO_2 and of HCO'_3, Cl' and H^+ ions, but not of Na^+ or K^+ ions.

Oxyhemoglobin is a stronger acid than reduced hemoglobin, and this plays a part in the *gas exchange:* In the lungs, the oxygenation of the hemoglobin acts as an acid and helps to expel CO_2; conversely, increase of CO_2 or lowering of the *p*H diminishes the affinity of hemoglobin and oxygen, and therefore raises the oxygen pressure in the capillaries. The carbon dioxide itself forms a readily dissociated combination with hemoglobin (*carbhemoglobin*), by a carbamino linkage, NH.COO, which binds and releases some 5 to 10 per cent of the total CO_2 of the blood. Finally, the corpuscles contain a catalyst, *carbonic anhydrase*, which speeds the dehydration of H_2CO_3 to CO_2. This is important for the prompt release of CO_2 in the lungs. If as much CO_2 as possible has been extracted from serum by a vacuum, considerably more is liberated by adding corpuscles, as if these acted like an acid (review, Roughton, 1935).

***p*H of Other Body Fluids.**—With few exceptions these have about the same reactions as the serum (Michaelis, 1914). Hanzlik, 1914, found the *p*H of *edema and pleuritic fluids* about 7.1; ascitic fluid, 7.42; *milk*, about 7; *cerebrospinal fluid*, between 6.98 and 7.3.

Human *sweat* is acid, with *p*H as low as 4.4, owing to fatty acids and to acid phosphates.

Digestive secretions have normally the following *p*H: *Saliva*, human, mixed, 5 to 8, generally about 6.9; fairly constant for the same individual, somewhat lower at night (L. I. Grossman and Brickman, 1937). *Gastric juice*, normal average, 1.77; *Intestinal* juice, 8; more alkaline in the ileum and colon than in the jejunum (de Beer *et al.*, 1935), the secretion of Brunner's glands is also alkaline (Florey and Harding, 1934). *Bile*, when flowing directly from the liver, is nearly neutral (0.07 to 0.2×10^{-7}). That from the gallbladder is more variable. S. Morrison *et al.*, 1938, report the following averages for normal gallbladder bile: dogs, 6.2; human, 7 to 7.5; rabbits, 8.8; guinea pigs, 8.9. It may become slightly acid on prolonged sojourn (Okada, 1915; Quagliarello, 1916).

The ***p*H of the contents of the digestive tract** may differ materially from that of the digestive juices, since these tend to be neutralized by each other, as well as by the buffer action of proteins. Bacterial activity may also introduce modifications.

Mouth.—The reaction may be made acid by regurgitation from the stomach, or locally by acid fermentation about the teeth. This may be a factor in dental caries, but its actual significance is in dispute (review, J. A. Marshall, 1939). *Gastric juice* has a normal average *p*H of 1.77.

Stomach.—The resting empty stomach may be nearly neutral. During the first one and one-half to three hours after a meal, the acidity rises rapidly to *p*H = 2 or even 1, depending on the individual. It then remains stationary until nearly all the food has left the stomach (McClendon, 1915). Excessive acidity is prevented by regurgitation of the duodenal contents (C. Bolton and Goodhart, 1936).

Duodenum.—The reaction of the duodenal contents is the resultant of the neutralization of the acid chyme by the slightly alkaline intestinal and pancreatic juice and bile. The actual *p*H of the duodenal contents is usually quite acid.

Myers and McClendon, 1920, found the usual reaction in man to be between *p*H = 3.2 and 5. With trained fistula dogs, Bollmann and Mann found the *p*H 7.5 when fasting, quiet and resting; on working with the dog, it soon became acid, 4.5; and in digestion 3.0. On feeding milk, it was generally about 5.0.

Small and Large Intestines.—The contents are normally slightly acid throughout the small intestines. The old opinion of the alkalinity of the intestines was based chiefly on unjustified deductions from the secretions. The *p*H of the human jejunum is from 3.8 to 7.8, mean 5.8 (Long and Fenger, 1917); the jejunum and ileum are probably from 6.0 to 8.0.

In hogs, Long and Fenger, 1917, found that the *p*H in the upper third of the small intestine ranged from 6.6 to 7.4, mean 6.7; in the middle third, 6.5 to 7.6, mean 6.9; in the lower third, 6.4 to 8.1, mean 7. Similar figures were obtained in calves, lambs and dogs. They have been confirmed by McClendon *et al.*, 1920, and by others.

Other mucous membranes generally approach neutrality. The *vagina* is an important exception, its normal *p*H being about 4.

The **reaction of urine** usually inclines toward actual acidity, the normal *p*H range in man being 5.12 to 7.46, the average about 6.03. The acidity decreases during the secretion of acid gastric juice, fasting and perspiration (Haskins, 1914). It exceeds 5 in less than 1 per cent and 5.3 in less than 10 per cent. The highest acidity reported is 4.7 (L. J. Henderson and pupils, 1914). The reaction is determined mainly by the ratio of phosphates. It may be readily altered by the administration of acids or alkalis, and is an important mechanism for regulating the acid: base balance of the body. The glomerular filtrate has the neutral reaction of the plasma. The acid reaction is effected by carbonic anhydrase (R. F. Pitts and Alexander, 1945); in the distal tubules if the acidification is moderate, extending to the proximal tubules if the acidity is high (P. Ellinger, 1940).

The **tissues** contribute but little to the buffering of the body (Brocklehurst and Henderson, 1927; Rous, Drury and Beattie, 1927).

The *p*H *of cells and tissues* is estimated as 6.6 for parenchymatous tissues, 7.2 for connective tissue (Rous *et al.*, 1927). *Muscle tissue* has the *p*H of 6.6 to 6.7, which is not altered by changes in the surrounding medium between 5.2 and 8.2 (Schmidtmann, 1924), but becomes acid in rigor. Impairment of circulation, as in *inflammation*, increases the acidity of tissues, as does *necrosis*. The *p*H of cytoplasm is from 6.8 to 7.2; that of the nucleus is from 7.6 to 7.8 (R. Chambers, 1942). In *hen's egg*, the *p*H of the yolk is 6.38, the white 8.70 (Capraro and Fornaroli, 1939). In large amebae the liquid of the vacuoles has a different reaction from the cytoplasm (Scarth, 1924). *Plant cells* may reach the acidity of *p*H 3, as shown by their colors, which are natural indicators (Haas, 1916). These have been utilized for observing the *penetration of acids into living cells.* E. N. Harvey, 1914, employed a holothurian, Stichopus; W. J. Crozier, 1915, a nudobranch, Chromodoris; A. R. Haas, 1916, used plants, pelargonium and blue hyacinth. Their results show that the penetration of acids into living cells is slight and does not depend simply on ionization, but that other factors are involved, such as the binding of the substance within the cell. M. Irwin, 1922, showed that the rate of penetration is generally inverse to the H ion concentration. Osterhout, 1914, had found that very dilute acids decrease the permeability of Laminaria, but that this increases when toxic concentrations are reached. The differences in penetration are illustrated by the *sensory effects,* the *sour taste,* or the retraction reactions of earthworms (Crozier, 1918), which are not strictly proportional to the *p*H. Weak acids and weak alkalis generally produce much more stimulation than would correspond to their *p*H. The threshold acid taste is 0.001N for hydrochloric acid; 0.00035N for acetic acid, and 0.00003N for carbonic acid; an efficiency ratio of 1:3:30. Dissolved *carbon dioxide* enters living cells much more readily than ionized acids, presumably as dissolved, unhydrated gas. By hydrating within the cell, to form $H.HCO_3$, it increases the H ion concentration more than does exposure to other acids (Jacobs, 1920; Osterbon and Dorcas, 1925). H_2S similarly enters as the undissociated dissolved gas and not as sulfide ions. Oxygen also enters cells freely (E. N. Harvey). Of *alkalis,* NH_4OH (or more probably NH_3) enters 90 to 100 times more readily into living cells than does NaOH; indeed, the latter enters practically only after injury (Haas, 1916). As ammonium penetrates much more readily than Cl ions, cells laid in NH_4Cl solution become alkaline, although the solution itself is acid (Jacobs, 1922).

The sour taste thresholds of hydrochloric and sulfuric acid solutions are not entirely parallel to their *p*H, so that some other factor enters (R. B. Malmo and Ellis, 1941).

Restoration of the Potential $H^{(+)}$ and $OH^{(-)}$ Ions.—The regulating mechanism of the blood is important for protecting the body against sudden changes, for meeting temporary emergencies. However, this impairs the stock of potential $OH^{(-)}$ and $H^{(+)}$ ions, and therefore would not furnish permanent protection. Other mechanisms are called into play to restore the normal ratio of these potential ions, mainly by regulating the excretion of CO_2 through the lungs, by varying the reaction of the urine, and by the more or less complete conversion of NH_4 into urea.

Regulation by Excretion of CO_2.—Addition of acid to the blood liberates CO_2 from the bicarbonate. This increases the CO_2 tension, and thus its excretion by the lungs. The increased CO_2 tension stimulates the respiratory center, and thereby hastens the elimination. This restores the normal ratio of $H_2CO_3 \div NaHCO_3$. Conversely, the addition of alkali diminishes the tension of CO_2 and thus its excretion.

Regulation by Combustion of Organic Acids.—The organic acids arising in metabolism are normally oxidized to CO_2 and H_2O, and excreted by the lungs and urine. This mechanism is disturbed in disease, starvation, and so forth, and then gives rise to acidosis. Conversely, the injection of alkali materially increases the excretion of unoxidized lactic acid by the urine (Macleod and Knapp, 1918).

Regulation by the Urine.—The urine, like the blood, contains a mixture of acid and neutral phosphates (Orth found a mean of 60 per cent as MH_2PO_4 and 40 per cent as M_2HPO_4). When acid is introduced, the ratio of acid phosphate is increased; alkalis increase the proportion of alkaline phosphate. This elimination of the excessive acid or alkali ions rapidly restores the potential acidity or alkalinity of the tissues. The flow of urine is also increased, so that acids and alkalis act as *diuretics.* The administration of acids first increases the PO_4 excretion; later, this decreases with the available supply of these ions (Fitz *et al.*, 1907). Under normal conditions, the human kidneys free the body of 60 to 70 cc. of normal acid per day. In diabetic coma, this quantity may be increased ten times (Henderson and Palmer).

Bicarbonate Regulation.—R. F. Pitts and Lotspeich, 1946, report a fixed renal threshold of about 25 millimols per liter of plasma, below which practically all the bicarbonate of the glomerular filtrate is reabsorbed. That above this concentration is excreted as a linear function of the plasma concentration, and is therefore relatively independent of the glomerular filtration rate.

Mineral Metabolism in Experimental Acidosis of Rabbits.—Goto, 1918, administered 25 to 75 cc. of N/4 HCl daily for one to four weeks. Most of the animals that received more than 25 or 30 cc. per day died within one to two weeks. The major alkali reserves were utilized in the following order: first the plasma bicarbonate; then the alkaline carbonate and phosphate of the muscles; and the calcium carbonate of the bones.

Regulation by Ammonium Metabolism.—In man and in the carnivorous animals the more or less complete conversion of the ammonium ion into the neutral urea also serves to regulate the alkali balance. If the acidity tends to rise, a larger part of the ammonium is left unconverted, and is used to neutralize the excessive acid. If the alkali tends to rise, more of the ammonium is converted, leaving its anion to neutralize the alkali. The ratio of unconverted ammonia (reflected in the ratio of NH_4 to total N of the urine) rises if acids are introduced (Walter, 1877), or formed in the organism (acidosis); and is lowered when alkalis are administered (Janney, 1911). After large doses of alkali, ammonium disappears completely from the urine. The administration of ammonium chloride increases the acidity of the urine, since the formation of urea releases unbalanced Cl^- ions, which convert Na_2HPO_4 into NaH_2PO_4 (Haldane, 1921).

Acidosis or acid intoxication arises clinically when the elimination of acid fails to keep step with its production. The inadequacy of elimination may be respiratory, circulatory, renal or metabolic, the latter by failure to burn organic acids to the more easily eliminated CO_2. Acidosis therefore occurs in asphyxia, in cardiac decompensation, in shock and with capillary poisons, nephritis and diabetes mellitus. It occurs also in healthy individuals by excessive exercise or by alterations of pulmonary ventilation. It may be induced by the administration of acids or acid-forming drugs. So long as there is an adequate store of potential alkali, the actual reaction of the blood is not materially changed, although its carbonate content is lowered. This decrease of reserve alkali without decrease of *p*H constitutes *compensated acidosis* (Rowntree, 1916). The diminished reserve probably alters the *p*H of the tissues, as it gives them less concentration gradient for buffering. The symptoms of acidosis develop and the acidity and the ammonium content of the urine increase. *True acidosis*, an actual fall in the *p*H of the blood below 7.4, occurs only when death approaches and the impaired respiration fails to remove the carbon dioxide. Actual acidity of the blood, with *p*H below 7, is not seen clinically.

The alkali reserve of the blood may be judged indirectly by the alveolar CO_2 tension, and by the "*alkali tolerance test*": When the bicarbonate of the blood is lowered, a larger dosage of alkali is required to change the reaction of the urine to alkaline than is the case normally. This increased tolerance for alkali is a delicate index of decreased potential alkalinity of the body and therefore of even slight degree of acidosis, including renal acidosis; and an equally reliable criterion of the progress of the acidosis and of the need of alkali therapy (Palmer and Henderson, 1913). It is misleading if there is marked renal insufficiency.

Ketogenic acidosis is a special type due to failure of complete combustion of the fatty acids with an even number of carbon atoms, the ketone acids, betahydroxybutyric, acetoacetic and propionic, and acetone. These are produced chiefly by the liver (Chaikoff and Soskin, 1928), as part of its fat metabolism, and burned normally by extra-hepatic tissues, especially muscle, as a source of energy (I. A. Mirsky, 1942). Their production is increased when additional fat is burned to take the place of deficient carbohydrate contribution (A. H. Neufeld and Ross, 1943). Part of the additional acid escapes combustion and passes into the urine (Stadelmann, 1883) and causes acidosis (Minkowski, 1888), including increased ammonium excretion. This occurs in starvation (Benedict and Osterberg, 1914) or on fat-rich diet, in diabetes mellitus when this is not adequately treated, and in hepatic disorders (Mottram, 1915; Woodyatt, 1916). Diabetic coma usually involves acidosis (Stadelman, 1883), and before the introduction of insulin it was treated with alkali (F. Walter, 1877; Magnus-Levy, 1899).

Ketone substances may also be formed from leucine and tyrosine, and therefore from protein, but not from carbohydrates. The agents that can give rise to the ketone substances are called *ketogenic;* those that tend to prevent this are *antiketogenic* (review, S. Soskin and Levine, 1944).

Toxicity of Ketone Substances.—Salts of the ketone acids stimulate the respiratory center materially more than salts of other organic acids (Tiemann, 1930). Ehrmann, Esser and Loewy, 1911, claimed that the injection of neutral oxybutyric salts produces coma, so that the diabetic coma would not be a pure acidosis.

Symptoms of Acidosis.—The first clinical sign of moderate acidosis is the hyperpnea, required to eliminate the liberated CO_2 (Douglas and Haldane, 1901; Winterstein, 1915). When the actual reaction of the blood becomes noticeably changed, the vasomotor and other medullary centers are also stimulated, especially if the change is acute, as with intravenous injection of acid. With further rise of the H ion concentration, the nervous centers become depressed, as does also the cardiac muscle. The effects agree with those of excessive CO_2 tension, asphyxia, oxygen deprivation, and diabetic coma, which are really forms of acidosis. The final symptoms are coma, convulsions, depressed respiration and fall of blood pressure. Death takes place by respiratory paralysis, generally before the blood becomes actually acid. The respiratory stimulation is mediated partly through the carotid sinus (Heymans *et al.*), but is chiefly a direct action on the respiratory center (C. F. Schmidt, 1932). Even if the *p*H of the blood is not altered, the diminution of reserve alkali may result in a local acidosis of the cells of the respiratory center, since the gas metabolism of nerve cells is nearly a hundred times as great as that of muscles (Alexander, 1912).

Role of H Ion Concentration and Carbon Dioxide.—In general, the respiratory stimulation is proportional to the H ion concentration (Winterberg; T. B. Robertson, 1912). However, carbonic acid stimulates more than would correspond to its acidity (Kopaczewski, 1914). R. W. Scott, 1918, found that excess of CO_2 stimulates respiration even if the blood is made distinctly more alkaline ($pH = 7.65$), as by sodium carbonate injection. The greater efficiency of carbonic acid is probably due to more ready penetration into the cells as CO_2, with subsequent hydration and ionization; so that it is toxic even from solutions in which it is buffered to neutrality (tadpoles, M. H. Jacobs, 1919; asterias and arbacia ova, H. W. Smith and Clowes, 1923). The factor of penetration probably also modifies quantitatively the action of *other acids*. The organic acids generally penetrate, as unionized molecules, better than do H ions.

Circulation.—Acidosis, especially when it is induced acutely, raises the blood pressure by stimulation of the vasomotor center, partly directly, partly by the carotid sinus reflex (Pilcher and Sollmann, 1915; Heymans *et al.*, 1932). The heart is affected through the blood pressure changes, the sinus reflex and venous return (review, Wiggers, 1929).

Intravenous injection of dilute acid produces flocculation of the plasma proteins, and therefore colloidoclastic reactions predominate over the acidosis. This has been employed against infections; but as the amount of flocculation cannot be controlled, it seems an undesirable form of nonspecific therapy.

In clinical practice, hydrochloric acid, 1:500 to 1:1000, is injected slowly, beginning with 2 to 3 cc. and increasing to 10 cc., every second to seventh day. It has been reported that it hastens recovery from aliphatic narcosis (McGilora, 1934), but the claim has not been confirmed by later workers (Shambaugh and Boggs, 1934; Kinard and Erve, 1935). The intravenous injection of 0.5 cc. of normal lactic or other acid per kilogram of dog produces, however, a marked increase of the rate and amplitude of respiration (S. J. Cohen, 1918). The *toxicity of acids* varies greatly according to conditions. In cattle, for instance, Berg, 1915, sometimes found considerable tolerance (0.87 Gm. of HCl as 0.9 per cent intravenously per kilogram).

The effects of pH on excised organs are important for experimentation, but not in the body, since they require greater changes of *p*H than occur during life.

Hydrogen Ion Concentration of Perfusion Solutions.—Distilled water, if carelessly prepared or if stored, becomes distinctly acid (*p*H about 6.3), and imparts this acidity to sodium chloride or glucose solutions prepared from it (J. R. Williams and Swett, 1922). The balanced solutions contain sufficient alkali to overcome this. The *p*H of Locke's solution is about 7.5, but it has a low buffer value. That of Tyrode's solution is 8 to 8.1 (G. G. Roth, 1917). Only bicarbonate can be used for buffering, as other buffer ions precipitate or disionize calcium.

Frog's Heart.—The automatic contractions continue only within certain ranges of H concentrations, which differ for the various portions of the heart (Dale and Thacker, 1913). The sinus requires the highest H ion concentration, the ventricles the lowest. O. W. Barlow, 1929, found *p*H 7.2 optimal for perfused frog heart.

Perfused Terrapin Heart.—Hydrogen ion changes within the physiologic range produce definite effects. *Increased alkalinity* (*p*H 7.6 to 7.8) increases tonus, especially of the auricles, and diminishes the excursions. *Diminished alkalinity* (7.3) increases the output, by increasing the amplitude of the beats and diminishing the tonus (Andrus, 1919).

Isolated Mammalian Heart.—The effects of oxidizing substances, acids and alkalis are described by Loevenhart and Eyster, 1913. Yanagawa, 1916, reported the coronary vessels constricted by increase of alkalinity, dilated by acidity. The *coronary vessels* of the perfused heart are dilated by acids, CO_2 being especially potent (Berthier and Gley, 1939).

Lymph Flow.—Yanagawa, 1916, found the thoracic lymph flow unaffected by the intravenous injection of acids, to the point of toxicity. Alkalis acted only like neutral salts.

Smooth Muscle.—Increase of acidity depresses, relaxing the tonus and weakening and slowing the rhythmic contractions. Higher concentrations produce death in the relaxed state. Increased *alkalinity* quickens the rhythm, but may diminish the excursions. The effects are independent of the innervation and are therefore directly muscular (Evans and Underhill, 1923).

Peripheral Action on Vessels.—Weak acids tend to relax and alkalis to constrict (Gaskell, 1880 to 1882; Schwarz and Lemberger). However, the *p*H changes necessary for these effects lie far outside the variations that can occur in the living body. Excised arterial rings do not respond satisfactorily to acid (I. Adler, 1916). Atzler and Lehrmann, 1921, claimed that the greatest dilatation of frog vessels occurs about *p*H 6. *Capillaries* are also dilated, but this also requires concentrations not reached in life (Krogh).

Excised intestines, of rabbits or cats, suspended in Ringer's solution are depressed progressively by increase of acidity. They are arrested about *p*H 6.2 to 6.0. If the acidity is produced by CO_2, recovery occurs more promptly when the neutral reaction is restored. Increase of alkalinity stimulates the intestine progressively up to *p*H 8. When added as $NaHO_3$, the stimulation is perceptible at 0.008 per cent, increases to 0.04 per cent, and becomes spastic about 0.08 per cent. Higher concentrations depress (Oettingen *et al.*, 1928). Gaseous CO_2 depresses frog's intestine in a moist chamber (Hooker, 1912). In intact dogs, intravenous injection of sodium bicarbonate (50 cc. of 2.5 to 6 per cent solution) produces stimulation (King and Church, 1922). *Excised uterus of guinea pig* has its response to pituitary stimulation decreased by increase of bicarbonate, and enhanced by CO_2 (Hastings and Van Dyke, 1927). *Excised ureter* movements are depressed by acid, stimulated by alkalinity (G. B. Roth, 1917). Alkalinity increases the motility of *spermatozoa* (Virchow, 1854); diminishes the rhythmic movements of *medusae* (Bethe, 1909); increases the resistance of *fundulus* to lack of oxygen (Packard, 1906). *Striped muscle* is relatively insensitive to small changes of *p*H. When immersed in somewhat higher concentrations of *acid*, there is an initial increase of tension, which is reversible; and then a slower, irreversible shortening, which constitutes rigor. These effects occur in narcotized muscle and are not conducted to parts of the muscle that are not immersed. They are due to precipitation of the muscle protein (Ranke, 1865; Burridge, 1910; Verzar *et al.*, 1922). Alkalinity beyond the physiological limit (*p*H = 9) increases the excitability of the *myoneural junction*, in frogs (M. H. Grant, 1920).

Metabolism.—The administration of nontoxic doses of acids and bases (to dogs) does not materially alter the balance of N, Ca, Mg or P (Givens and Mendel, 1917). It alters the ammonium metabolism. Acidosis tends to *mobilize calcium*, lead and similar elements from *trabecular bone.*

Doses as large as 13 Gm. of sodium carbonate, 20 Gm. of sodium bicarbonate, or 40 Gm. of sodium citrate do not influence the total nitrogen excretion. Macleod and Haskins, 1906, found increased elimination of endogenous *uric acid* and purines. Abl, 1913, attributed this to the intestinal derangement. The alkalis, especially potassium bicarbonate, acetate and citrate, had some reputation *in acute and chronic rheumatism*, and gout, but their efficiency is questionable. There is no good foundation for the assumption that they increase the oxidation of uric acid or its solubility in the tissues.

The **use of alkalis against acidosis** requires rather large doses, administered as sodium bicarbonate or acetate or citrate. For long-continued administration, it may be supplemented by calcium carbonate and magnesium oxide. The carbonate can take up more carbonic acid than bicarbonate, but this advantage is illusory, for the ratio of carbon dioxide and carbonate is immediately adjusted in the lungs to the normal equilibrium (Sellards).

Administration and Dosage in Acidosis.—The use of alkali should begin as soon as the acidosis is recognized and not delayed until coma has set in, for it may then be too late. The initial daily dose of sodium bicarbonate by mouth may be 30 to 45 Gm., in divided doses and freely diluted, best between meals. This may be raised to 100 Gm. or more. (The equivalent of 30 Gm. of sodium bicarbonate by oral administration is furnished by each of the following: sodium acetate or citrate, 40 Gm.; calcium carbonate, 15 Gm.; magnesium oxide, 7 Gm.)

After coma has set in, 4 per cent sodium bicarbonate solution may be administered by the drop enema; but this may not secure sufficient absorption, and then requires to be supplemented by intravenous injection, generally of 5 per cent bicarbonate. Generally, 500 cc. (containing 25 Gm.) injected slowly during half an hour is a safe maximum (Sellards). Larger amounts cause tetany. If the solution is sterilized by boiling, it loses CO_2 and forms carbonate, which produces hemolysis, perhaps also calcium flocculation. It would cause serious sloughing if it escaped into the subcutaneous tissue. A boiled solution may be restored to the proper reaction by passing CO_2, or adding HCl, until it is colorless to phenolphthalein.

Intravenous bicarbonate in shock and dehydration were thought to give better results than plain saline infusion, the rise of blood pressure being more sustained and the respiration deeper (Seelig *et al.*, 1913); but excessive doses of alkali result in alkalosis, and the advantages of intravenous injection are now considered doubtful.

Asiatic cholera results in considerable loss of reserve alkali, with the production of acidosis. It is benefited by the early administration of sodium bicarbonate, increasing the dose with the severity of the symptoms (Sellards, 1914). According to Brouardel ("Les Asphyxies," p. 11) alkaline saline intravenous infusions were successfully used in algid cholera by Lorain, 1866.

Alkalosis consists in excessive *p*H or bicarbonate, or both, in the plasma. It may arise clinically from excessive administration of alkali, especially of sodium bicarbonate as in the treatment of peptic ulcer; or from salts of organic acids which are burned to carbonate in the body. Fruits and green vegetables increase the alkali reserve. Alkalosis occurs also from the loss of HCl through persistent vomiting, progressing to fatal tetany (McCann, 1918; Hastings, Murray and Murray, 1921), and in nephrosis with hypertension even on a normal alkali income (Way and Muntwyler, 1930).

The *clinical symptoms of alkalosis* generally appear some ten days after beginning alkali treatment, with nausea and distaste for food, then headache of increasing severity, and weakness. More severe degrees develop *tetany*, uremia, edema and delirium. The plasma *p*H is high unless the alkalosis has been compensated. Plasma bicarbonate is high if the cause is excessive alkali income; it is normal or low in hyperemesis. The plasma chloride is decreased, the nonprotein and urea nitrogen are increased. The urine is alkaline and often contains albumin. The hemoglobin holds its oxygen more firmly than normal (Barcroft), tending to anoxia of the tissues. The kidney injury contraindicates the employment of large doses of sodium bicarbonate (not of calcium carbonate and magnesium oxide) in renal disease, especially since this impairs the elimination of the alkali and therefore tends to exaggerate the alkalosis.

Compensation of alkalosis is fairly efficient, so that serious degrees are not common even with rather reckless alkali administration, if the kidneys are sound. It is accomplished chiefly by the excretion of alkaline urine, increasing the ratio of its Na_2HPO_4 to NaH_2PO_4. This is aided by more complete oxidation of ammonium, by neutralization of proteins and by increase of unoxidized organic acid, especially lactic acid.

The injection of *lethal doses* of alkali produces tremors, rigidity; finally vomiting, convulsions, relaxation of sphincters; sometimes edema and ascites (Rowntree, 1916). An excessive intravenous injection of bicarbonate, in a human subject, was followed by tetany, with recovery (Harrop, 1919).

Therapeutic modification of urine reaction is used incidentally as *indicator* for the treatment of acidosis and alkalosis. The administration of either acid or alkali salts increases the *urine flow*, often considerably. Acid salts are markedly adjuvant to the diuretic effect of the mercurials, caffeine group and posterior pituitary solution (Tiffeneau *et al.*, 1931). Acidification of the urine renders it less favorable to *bacterial growth*, and greatly enhances the antiseptic potency of a number of other urinary antiseptics, especially methenamine and mandelic acid. Some mixed urinary infections resistant to acidification yield to *alternation*, every five to ten days, of acid and alkali reaction; but the efficiency is restricted, perhaps questionable. Acid urine irritates the bladder when this is inflamed, and alkalis give relief. Urate, oxalate and cystine *calculi* form only in acid, and phosphate calculi in alkaline urine. When they are present, or when the urine contains them habitually, the reaction that favors their formation must be avoided. The opposite reaction prevents their growth, although it does not dissolve those already formed (G. D. Oppenheimer and Pollack, 1937); alkalinization may, however, disintegrate the mucus and fibrin that cement them, and thus sometimes secure their evacuation.

Acid Irrigation of Phosphatic Renal Calculi.—These dissolve, although slowly, in 0.06 per cent HCl. Since this strength would be harmless, Geisinger *et al.*, 1918, suggested its use by continued irrigation, for stone in the renal pelvis or ureter. *Malic acid*, 1 to 3 per cent, has given some success, but continuous irrigation produces vesical and ureteral spasm (L. D. Keyser, 1935). *Sodium hexametaphosphate* is reported as the best solvent *in vitro* for phosphatic renal calculi (D. R. McCullagh *et al.*, 1941). *Magnesium citrate* solution may be used (H. J. Suby and Albright, 1943).

Ureter Flow.—In excised kidneys of rabbits, perfused with sodium chloride solutions, the ureter flow varies niversely to the H ion concentrations (Isaacs, 1917). In life, however, the conditions are much more complex.

Therapeutic Acidification of the Urine.—The reaction of the urine may be altered toward the acid side by the administration of mineral acids, but their scope is limited by their local actions. Larger changes are practical by the use of acid salts, such as sodium biphosphate, which combine considerable potential with a relatively low actual acidity; or by the administration of ammonium chloride, which leaves an excess of unbalanced chloride ions when the ammonium is dehydrated into the urea; or by ammonium biphosphate in the same dosage, which secures both actions (Alstead, 1936); or by calcium chloride, which also gives an excess of Cl ions, because part of the calcium is precipitated as carbonate in the intestines. All these are given in doses of 1 to 2 Gm., 15 to 30 grains, three to four times per day, in water or milk. The acidification of the urine does not surpass the normal upper limit.

For instance, the administration of the maximal dose of acid sodium phosphate raised the acidity from *p*H 6.7 to 5.8 (L. J. Henderson and Palmer, 1913); and from 7.2 to 4.85 (Hanzlik and Collins, 1913). Benzoates have a tendency to render the urine acid (Jordan, 1913); also boric acid, 2 Gm. daily (G. G. Smith, 1913); but these are not advised for therapeutic use.

Mandelic acid, $C_6H_5CH(OH)COOH$, was introduced by M. L. Rosenheim, 1935, as a practically nontoxic keto acid which is excreted unchanged in the urine and renders this bacteriostatic, especially if the reaction of the urine is kept fairly acid and the water intake limited. It is successful against some obstinate nonspecific urinary infections which resist sulfanilamide. Its occasional untoward actions are not serious, if it is used carefully, but it should not generally be employed when there is renal insufficiency (review, Braasch, 1937).

Historical.—A. L. Clark, 1931, 1935, reported the efficacy of ketogenic diet (poor in carbohydrate and rich in fat) in urinary infections, but as such diets tend to derange digestion and are difficult to apply this was considered a last resort, when all other measures had failed. A. T. Fuller, 1933, showed that the bacteriostatic effect of ketogenic diet is due to a special bactericidal action of *free betahydroxybutyric acid.* To be effective, this requires at least 0.5 per cent of the acid and *p*H of 5.5, and becomes more potent with increase of the acid and acidity (Helmholz and Osterberg, 1936). This suggested experimentation with other keto acids to Rosenheim.

Administration.—Mandelic acid is bactericidal to most organisms when its concentration in the urine is $\frac{1}{4}$ to 1 per cent, and the *p*H 5.0 to 5.7 (Helmholz and Osterberg, 1936). These conditions are secured clinically by the oral administration of 3 Gm. of mandelic acid four times daily, before meals and at bedtime; or preferably calcium mandelate, 2 Gm. every four hours for six doses daily; together with 4 to 8 Gm. of ammonium chloride per day, to acidify the urine; or ammonium mandelate may be administered directly, 3 Gm. three times daily in water. The taste of mandelates is unpleasant and difficult to disguise. Sodium mandelate may be given intravenously if there is much digestive disturbance (G. Caroll and Coleman, 1943).

Concentration of the mandelic acid must be secured by limiting the fluid intake to five glasses or less per twenty-four hours; failure is likely if this is neglected. The *p*H of the urine must be checked daily and kept at 5.5 or less, by administering additional ammonium chloride. With these conditions the urine usually becomes bactericidal within two or three days, and free from bacteria in six or seven days. It is rarely necessary to continue beyond twelve or fourteen days. If further administration appears advisable, a rest period of one or two weeks should be interposed as precaution against irritation. The treatment is successful in some 80 per cent of uncomplicated urinary infections, and some of the others are considerably improved. It is apparently most effective against coli and proteus ammoniae, and less so against staphylococci and pyocyaneus (Caroll *et al.,* 1936). It is more effective than sulfonamides against streptococcus fecalis. Even partial success is valuable in preparing the urinary tract for instrumentation and surgery. It acts only on the excreted urine, and not on the deeper tissues. *Untoward effects* are not common, nor serious. *Nausea* occurs in less than 1 per cent and is less severe than with ketogenic diet, but may force discontinuance with a few patients. *Diarrhea* occurs in some 10 per cent, but is unimportant. *Hematuria* (L. P. Dolan, 1936) is common but rarely gross, and ceases on suspending the drug. *Renal irritation* is doubtful; but a few hyaline casts are common, and dogs show a temporary rise of nonprotein nitrogen in the blood, after intravenous injection. Liver damage (fatty degeneration, especially of the Kupffer cells) has been reported; it may be due to an oxidation product, benzoylformic acid. Hepatic insufficiency is a contraindication, and administration should be stopped if icterus occurs (K. Meier, 1940).

Urinary Antiseptics.—The urine and the bladder may be disinfected to a considerable degree by drugs administered through the mouth. The efficiency of urinary antiseptics is naturally limited by the brief contacts. Comparative studies of their clinical efficiency were made by E. Davis and Sharpe, 1932, and N. F. Miller and Chu, 1934, the latter especially on the influence of water intake. Methenamine is highly effective in acid urine. Acriflavine is effective if the urine is alkaline. Hexylresorcinol is independent of the reaction, but of uncertain efficiency. Pyridium is generally ineffective. Sodium salicylate or benzoate, or salol, copaiba, cubeba, sandal wood and methylene blue were used against gonorrhea, and santal oil against staphylococci, but none of these are very effective (Hinman, 1915). Increased acidity of the urine also destroys bacteria. Dilute mineral acids, or acid sodium phosphate, may be used (Jordan, 1911), or a ketogenic diet. Periodic alteration of acid and alkali administration may be more effective. Penicillin and sulfonamides are especially effective in gonorrhea.

PREPARATIONS.—***Mandelic Acid,** U.S.P., racemic phenyl-glycolic acid. White crystalline powder. Gradually darkens and decomposes on exposure to light. Soluble in 6.5 parts of water, freely soluble in alcohol. Dose, 3 Gm. *Calcium Mandelate,* U.S.P., is only slightly soluble in cold water. Dose, 4 Gm. *Syrup Ammonium Mandelate,* N.N.R., corresponds to about 4 Gm. of mandelic acid in 10 cc. of the syrup.

Ketogenic diet in epilepsy has given variable results. Helmholz, 1930, reported 30 per cent freed from attacks, 20 per cent improved, 50 per cent unaffected. Notkin, 1934, observed increase in the number of convulsions in eighteen of twenty patients. Apperly and Norris, 1933, found that it produced alkalemia in three normal women. H. M. Keith, 1933, reported that injection of sodium acetoacetate prevents thujone convulsions in rabbits; also organic or hydrochloric acids, but less potently. To obtain the ketone effects, carbohydrates must be reduced to less than 20 or 30 Gm. per day, proteins to less than 60 Gm., and the ratio of molecules of fat to dextrose must be higher than 2:1. *Petit mal* and psychomotor seizures associated with slow-wave electrograms respond better to ketogenic diets. This may be connected with the acidosis, for promising results are reported for *dl-glutamic acid hydrochloride,* which has no effect on grand mal seizures (J. C. Price, Waelsch and Putnam, 1943).

Therapeutic Alkalinization of the Urine.—The administration of alkalis can increase the alkalinity somewhat beyond the normal range; *i. e.*, 20 to 40 Gm. of $NaHCO_3$ per day produced a maximal alkalinity of *p*H 8.7 (Henderson and Palmer, 1913); 4 Gm. changed the reaction from *p*H 6.5 to 7.4 (Hanzlik and Collins, 1913). About 5 to 10 Gm. of $NaHCO_3$, or 10 to 15 Gm. of sodium acetate or citrate, per day would be required to keep the urine of a normal individual alkaline. The acetate and citrate have an advantage in not upsetting the reaction of the digestive tract. For the urinary effect, alkalis should be taken especially at bedtime, since the night urine is most acid; not at mealtime, because the urinary acidity is lowest during digestion.

Alkali Injection in Nephritis.—Energetic alkaline therapy was advocated by M. H. Fischer, who conceives nephritis and edema as acidosis. The clinical results in the hands of others have often been unfavorable and sometimes dangerous (Newburgh, 1913). Renal injury spontaneous glomerular nephritis of dogs) renders the acid-base equilibrium unstable, so that it is easily upset by anesthesia, especially by chloroform. This results in more severe nephritis, anuria or failure to respond to diuretics (MacNider, 1918).

Bicarbonate Edema.—Large doses of sodium bicarbonate (about 20 Gm. per day) may lead to the retention of water and eventually to edema, in proportion to the dose (Hayem, 1890). This may occur in diabetic as well as in normal individuals (Beard and Rowntree, 1917). It is probably analogous to salt edema.

Alkalis and Salicylates.—The administration of sodium bicarbonate with inorganic salicylates tends to prevent the precipitation of the irritant salicylic acid in the stomach. It has been affirmed that it would also prevent the albuminuria and acetone that sometimes follow salicyl administration (Glungen, 1911); but it is ineffective for this purpose (Hanzlik).

Alkalis and Cinchophen.—These are often prescribed together, with the view of preventing the precipitation of the increased uric acid in the urine.

Local Actions.—Concentrated acids and alkalis are corrosive by destroying protein. *Dilute acids* precipitate protein and are therefore *astringent* and *styptic* (Hanzlik, 1918). Saturated or half-saturated solution of boric acid is used on congested mucous membranes, especially in *conjunctivitis.* Slightly more concentrated acids are irritant. Vinegar is applied locally to harden the skin in *hyperidrosis.* Salicylic acid and benzoic acid are used in dermatology to stimulate the skin and slowly to dissolve calluses. *Sodium carbonate* is strongly irritant, and corrosive if the contact is prolonged. *Dilute alkalis* swell and dissolve protein, particularly *mucus*, and at the same time increase mucus secretion through a mild irritation. Sodium bicarbonate or borate is useful as washes or gargles (1 to 4 per cent) in *catarrhal conditions;* as expectorants; in cystitis, dysentery, and so forth. The false membranes of diphtheria, croup, and the like, are composed largely of mucus, and may be broken down by alkalis. These may be applied by inhaling the vapors produced by slaking lime in the sickroom. Alkalis are applied to the *skin* to soften the crusts in eczema; as a soothing lotion in dermatitis and burns; and to relieve itching.

The **digestive tract** is largely governed by the hydrogen ion concentration of its contents, as to its motor activities, secretions, ferment actions and bacterial flora. This is especially important in the stomach and the adjacent duodenum. The administration of moderate quantities of dilute acid or alkali has little or no effect, however, on normal digestion, because they are buffered by the mucus and readily compensated by the secretions. They become important when the digestive tract, especially the stomach and duodenum, is not normal. **In the mouth,** acids have a characteristic "*sour*" taste, and are slightly astringent. This taste determines their use as flavors. They soften the enamel of the *teeth*, and should therefore be taken through a glass tube. They reflexly increase the flow of saliva, but this is of little practical importance. The addition of acid makes it easier to take larger quantities of cold water than could conveniently be taken without. They are therefore of therapeutic value in *fevers*, to obtain at the same time the refrigerant action of cold and the diuretic effect of large quantities of fluid.

In the stomach, acid is important for the digestion of proteins and connective tissue; for its antiseptic properties; and for the elaboration of the anti-anemia fraction.

Gastric Acidity.—Pure human gastric juice is normally secreted with about 0.4 to 0.5 per cent of free HCl (Roeder, 1905; Rehfuss and Hawk, 1914; Carlson, 1915), the same as in dogs or cats. This corresponds to *p*H = 0.95 to 1 (Menten, 1915). This acidity, however, is not normally maintained in the stomach, the acid being rapidly neutralized by the saliva, the mucus and the reflux of duodenal contents, to 0.15 or 0.2 per cent HCl (Boldyreff). The breaking down of this mechanism appears to be the basis of "hyperacidity," in which the acid remains at the same concentration (0.5 per cent HCl) at which it was secreted (Carlson, 1915). The curve of the acidity during normal digestion was studied in man by McClendon, 1915.

The secretion of the gastric hydrochloric acid is confined to the parietal cells, where it first appears either in the cytoplasm immediately adjacent to the intracellular cananiculus, or in the cananicular wall (F. Hollander, 1943). The parietal cells have a high content of carbonic anhydrase (H. W. Davenport and Fisher, 1938), which converts their metabolic CO_2 into H_2CO_3. This exchanges with the NaCl of the plasma to form HCl and $NaHCO_3$ (J. S. Gray, 1942).

The *secretion of gastric* juice is normally provoked by the psychical and chemical processes connected with eating. Acid secretion may be stimulated especially by *histamine*, and by an analogous substance, *gastrin*, formed in digestion. The ingestion of dilute *acid* also increases the secretion of gastric juice. This effect is partly reflex, for it is observed in Pavlov's separated stomach (Bickel, 1905), but only when the acid is given with food (Heinsheimer, 1906). It was formerly believed that gastric secretion is also stimulated by the administration of alkali, but later experiments indicate that it is rather diminished both in quantity and acidity (Pavlov, 1897; Chiari, 1915).

In the duodenum, acid causes the secretion of mucus (Florey and Harding, 1934). It provokes the secretion of pancreatic juice, through the formation of secretin (Bayliss and Starling, 1902). It also causes increased secretion of bile and contraction of the gallbladder (Okada, 1915).

The threshold of duodenal acidity for stimulating pancreatic secretion in dogs lies about *p*H 5, and is greater at *p*H 4, which is commonly present in meat digestion (J. E. Thomas and Crider, 1940). Introduction of acid into the duodenum inhibits gastric secretion if the acidity exceeds *p*H 2.5 (I. J. Pincus *et al.*, 1942).

Digestive Action.—Pepsin acts only in the presence of *free acid.* Any acid may answer for this purpose; hydrochloric is most efficient in the concentration existing in the gastric secretion; it also aids in the *solution of the connective tissue of meats* and determines the *antiseptic* qualities of gastric juice. Most other digestive ferments are favored by slightly acid reaction, but trypsin can act in a weakly *alkaline* medium. Pepsin is inhibited or destroyed by alkalinity (Hamburger, 1915). Diastases are hindered by free alkali, and are indeed sensitive to it.

Salivary Digestion in the Stomach.—Slight acidity accelerates the action of all diastases, but somewhat stronger concentrations depress. However, the bulk of the food remains for an hour or more in the cardiac pouch, with only the surface layer impregnated by acid (Heyde and Gruetzner). Salivary digestion proceeds practically undisturbed during this time (Cannon, 1911).

Digestive leukocytosis may be produced by the introduction of dilute HCl into the empty stomach and therefore need not involve the digestion of proteins (Cathcart, 1923).

The discharge of gastric contents was believed to be controlled chiefly by the acidity of the gastric acid duodenal contents, acting on the pyloric sphincter (W. B. Cannon, 1911). Improved investigative methods show that this is erroneous. The emptying is accomplished by the peristaltic pressure gradient from the stomach to the duodenum. The pyloric sphincter is generally open and acts in the same direction as the bulb and antrum. They are important chiefly for preventing reflux of the duodenal contents. Acid food in the duodenum and emotional states delay emptying by depressing gastric motility, not by pyloric spasm (J. P. Quigley, 1943). *Administration of therapeutic doses of hydrochloric acid* (2 cc. of dilute acid in 100 cc. of water) has no significant effect on the gastric emptying time of healthy young men. *Sodium bicarbonate* (5 Gm. in 100 cc. of water) shortens the time by an average of 16 per cent. An equal effect results from disodium phosphate, 4 Gm. in 100 cc. (E. J. Van Liere and Sleeth, 1940). Dilute solutions of alkalis leave the stomach promptly; *hypertonic solutions*, whether acid or alkaline, do not pass readily from the stomach into the intestines (T. Grier Miller, 1939).

Perversions of Gastric Acidity.—The *p*H of gastric juice is not so constant as is commonly supposed. The free acid may range normally between 0.05 to 0.5 per cent HCl; in achlorhydria it is reduced to practically nothing, and with gastric ulcer it may rise to 1 per cent (K. P. Becker *et al.*, 1934, 1935). *Achlorhydria* is an important feature of pernicious anemia. *Hyperchlorhydria* occurs in nervous dyspepsia and gastric ulcer. It is due to retention of the acid in the stomach by pylorospasm, more than to increased acidity of the secretion itself. The prolonged acidity is probably an element in the development of peptic ulcers (Mann and Williamson, 1923; L. R. Dragstedt, 1935; Wilhelmj *et al.*, 1936).

The *pain of gastric ulcer and of hyperchlorhydria* is not due directly to increased acidity, but to hyperesthesia toward the ordinary acidity, and to muscular spasm, which is felt as painful only when free acid is present, not when this is neutralized (W. L. Palmer, 1943). "*Heart burn*" probably arises from regurgitation into the esophagus, which is sensitive to ordinary acidity (W. C. Alvarez, 1944).

In human subjects with normal stomachs, J. E. Schmidt, 1909, found no symptoms with 0.5 to 2 per cent HCl. With 5 per cent, Boring reports a sensation similar to hunger pains. The results on patients with gastric ulcer are more variable. Pain was sometimes, but not always, present after 0.1 to 0.4 per cent HCl. Ginsberg *et al.*, 1916, found that the pain is always accompanied by strong contractions, indicating that it is due to tension. This was relaxed by alkalis or amyl nitrite, strengthened by pituitary. L. L. Hardt, 1918, found that ulcer pains occurred in the absence of free acid and may sometimes even be relieved by 0.3 per cent HCl.

Through a gastric stoma in a normal man, S. G. Wolf and Wolff confirmed that no pain is felt from the healthy stomach on pinching with forceps, faradic stimulation, moderate distention, or on applying 50 and 95 per cent alcohol, $\frac{N}{1}$ HCl, $\frac{N}{10}$ NaOH, or mustard suspension; but severe pain results from these agencies when the mucosa is inflamed.

Use of Acids in Indigestion.—Acids are administered in dyspepsias in which the secretion of acid is deficient; in the achylia of pernicious anemia; in putrefactive fermentation; and in infantile diarrheas due to this cause. All mineral acids act alike. Dilute hydrochloric acid (1 cc., diluted, just before or after meals) is generally preferred. It is often combined with bitter stomachics. Doses much greater than the ordinary would be required to restore the normal acidity, but when taken after meals the acid would be confined to the surface of the food mass and would therefore suffer little dilution. The increased flow of pancreatic juice and of bile is probably too small to be of any value. Acids are *contraindicated* in catarrhal conditions. Even in normal individuals the prolonged administration of large quantities of acids is likely to prove too irritant, and interferes with digestion. This led to the popular use of vinegar to reduce *obesity*.

Administration of Alkalis on Normal Digestion.—E. J. Van Liere and Sleeth, 1940, found that 5 Gm. of sodium bicarbonate shortens the gastric sojourn of normal men. W. L. Adams *et al.*, 1943, report increased gastric pouch secretion in dogs; but the effects of moderate doses are not important in normal individuals. The utilization of food remains practically perfect. *Very large doses* inhibit gastric movements more or less completely (W. H. Dickson and Wilson, 1924) and cause diarrhea.

This may explain the use (or rather misuse) of alkalis in *obesity*. Full doses of alkalis temporarily lower the arterial pressure, probably as a result of the nausea. Scheffer, 1908, advocated sodium silicate for this purpose in *arterial hypertension;* bicarbonate accomplishes the same result, but the benefit is questionable. *Strong alkalis*, including sodium carbonate, cause gastritis.

Alkalis in digestive disorders are useful to dissolve excessive mucus, but particularly to neutralize hyperacidity. Sodium bicarbonate acts most promptly, magnesium oxide and carbonate produce a more lasting action and are laxative. Calcium carbonate is constipating.

Gastric Hyperacidity; Functional Dyspepsias, Heart Burn; Gastric Flatulence, and Similar Conditions.—In these conditions, the soluble alkalis (sodium bicarbonate or aromatic ammonia) are commonly used and effective. They neutralize the excessive acid, relax the spasmodic pylorus (Enriquez, Binet and Gaston Durand, 1914) and thus empty the stomach and lessen the pain and irritation. The liberated CO_2 stimulates the gastric movements (Schierbeck, 1891), and promotes the expulsion of the gas. It acts perhaps also as a mild local anesthetic. The bicarbonate is usefully combined with an aromatic carminative (peppermint) and cathartic (rhubarb). The *time of administration* has given rise to much theoretical and unproductive discussion. The alkalis should evidently be given when the digestive conditions call for them. This is better recognized by the symptoms than by rules. The soluble alkalis (bicarbonate, 1 Gm.; aromatic ammonia, 2 cc.; for infants, lime water) should be administered whenever they are indicated by gastric distress, and repeated as often as needed; also at bedtime and on arising. For intestinal effect, they should be given on an empty stomach.

Gastric ulcer is treated with closely spaced doses of alkali so as to prevent the gastric contents from becoming acid.

In the *Sippy routine* (1915), milk or soft food is given every hour. Midway between the feedings the patient receives an alkali, alternating between (1) magnesia and sodium bicarbonate, each 0.65 Gm., 10 grains, and (2) bismuth subcarbonate, 0.65 Gm., 10 grains, with sodium bicarbonate, 2 Gm., 30 grains. The progress is controlled by the reaction of the stomach contents. The alkali treatment of peptic ulcer might be expected to favor the formation of *urinary calculi*, and Eisele, 1940, found that 11 per cent of a series of patients with renal or ureteral calculi had received courses of alkali for peptic ulcer or other chronic digestive derangements; but H. L. Kretschmer and Brown, 1939, found this to be so in only 1.2 per cent of their calculi.

Intestinal catarrhs are also treated with alkalis, but the results are less striking. Neutralization of gastric acidity would protect the duodenum. Only the slowly soluble alkalis, magnesium oxide or carbonate or calcium carbonate, could have any effect on the reaction of the lower levels of the intestines, and there the laxative or constipating action of their cations is more important than their alkalinity.

Enemas, of 1 per cent sodium bicarbonate (a teaspoonful to a pint), are used for cleansing and in mucous colitis.

The *intestinal bacterial flora* may be utilized to acidify the intestinal contents. This is sometimes effective against persistent intestinal putrefaction. Implantation of lactic acid organisms by oral administration has not proved successful. Better results are obtained by feeding lactose. The beta variety is more effective than the alpha (C. R. Robinson and Gilliand, 1937).

Preparations.—Official dilute mineral acids have a uniform strength of 10 per cent. They are colorless, odorless liquids, of strongly acid taste; miscible with water, alcohol or glycerin. They are *incompatible* with alkalis and the salts of weak acids (carbonates, salicylates, sulfides, sulfites, and so forth). *Dose,* 1 to 2 cc., 15 to 30 minims, diluted.

***Dilute Hydrochloric Acid,** U.S.P., is the most commonly employed. Dose, 2 to 4 cc. (30 to 60 minims) in half a glass of water, taken through a glass tube to avoid corrosion of the teeth; it may be repeated in half an hour. In *pernicious anemia*, to 4 cc. four times daily, with meals. *Aromatic Sulfuric Acid* is an alcoholic dilution of sulfuric acid, flavored with ginger and cinnamon. Contains free sulfuric acid and ethylsulfuric acid equivalent to about 20 per cent of H_2SO_4. A clear, reddish-brown liquid; pleasant aromatic odor; intensely acid. Dose, 0.5 cc., 8 minims, diluted. It is doubtful whether it has any advantage over other acids. Ethylsulfuric acid acts simply as a mineral acid (Uyedo, 1910).

***Sodium Bicarbonate,** U.S.P. (Baking Soda), is a white, odorless powder; of cooling, mildly alkaline taste; permanent in dry air, but slowly decomposes in moist air. Sol in water, 1:10, practically without decomposition. When heated, it loses CO_2, and is converted into normal carbonate. Practically insol. in alc. Incompatible with acids and acid salts, and with the salts of most alkaloids, metals and earths; not with magnesium salts in moderately dilute solutions. Dose, 1 to 4 Gm., 15 to 60 grains. "*Soda Mint*" tablets generally contain 5 grains, with $\frac{1}{8}$ minim of oil of peppermint. *Potassium Bicarbonate,* U.S.P., has similar properties, but is more soluble in water (1:2.8). *Potassium Carbonate,* U.S.P., is even more soluble (1:1).

ORGANIC ACIDS AND THEIR SALTS

Acetates and formates are easily absorbable salts, with simple ion actions. Tartrates, citrates, lactates and malates are not easily absorbed and therefore act as saline cathartics. The free acids are relatively feebly dissociated and therefore produce relatively mild acid effects on the skin and mucous membranes and in the digestive tract. They are burned more or less completely to carbon dioxide and water (Buchheim, 1888). Their salts therefore are administered to combat acidosis or to render the urine alkaline, with avoidance of acid effects in the digestive canal. They also cause saline diuresis. Sodium citrate forms a double, nonionized salt with calcium, and so prevents coagulation when added directly to the blood. Free citric and tartaric acid are used mainly for flavoring and for producing effervescence with carbonates. Lactic acid is employed as mild caustic for the solution of false membranes, and in laryngeal tuberculosis. Formic acid is used as counter-irritant.

Nutrition and growth are markedly impaired if rats are given 0.25 per cent acetic or formic acid as their sole drink; 0.5 per cent causes loss of weight as rapid as with complete starvation (Sollmann *et al.*, 1921).

Acetylation of sulfanilamide is increased by administration of acetate, pyruvate, lactate, glucose and alcohol (J. Fraenkel-Conrad and Greenberg, 1946).

When injected intravenously as sodium salts into nephrectomized dogs, acetate disappears most rapidly from the circulation, then butyrate, caproate, and caprylate, indicating that they are metabolized in this order (J. A. Dye and Babcock, 1943). Tracer experiments with heavy hydrogen show that acetate is used in synthesizing *cholesterol;* propionate, butyrate, succinate, pyruvate, and acetoacetate are not (K. Bloch and Rittenberg, 1942). Rats fed with sodium *acetate* containing deuterium in the methyl group utilize this in the synthesis of fatty acids (D. Rittenberg and Bloch, 1944). Liver and kidney slices readily oxidize acetate chiefly through the intermediate formation of acetoacetic acid, by coupling two acetyl groups. Slices of heart tissue oxidize without forming acetoacetic acid, and this may occur to a minor degree with liver and kidney slices (S. Weinhouse *et al.*, 1945).

The *antacid action* is exerted only by the oxidation of the absorbed salts. The CO_2 formed from the free acids would be exhaled. The ordinary antacid dose of sodium acetate or citrate is about 15 Gm. per day, freely diluted.

Sodium acetate is probably the least disagreeable, but some prefer mixtures, such as potassium citrate, 1 Gm.; sodium bicarbonate, 2 Gm.; sodium acetate, 3 Gm.; this dose three times daily. Potassium salts are deliquescent and should therefore not be dispensed as powders. Such mixtures were formerly prescribed against *rheumatism* and *gout.*

ACETATES

Potassium and sodium acetates are used mainly as alkaline diuretics and to counteract acidosis. The toxicity of sodium acetate is low, even on intravenous injection. Free acetic acid acts locally simply as a feeble acid.

***Sodium Acetate,** $NaC_2H_3O_2 \cdot 3H_2O$, occurs as colorless crystals or granular powder; odorless; saline taste, efflorescent. Sol. in water (1:0.8). Dose, 1.5 Gm.; to alkalinize urine, 5 to 10 Gm. per day. *Potassium Acetate,* U.S.P., deliquesces and should not be dispensed in powders. Dose, 1 Gm., 15 grains, diluted. *Acetic Acid* contains about 36.5 per cent of absolute acetic acid; *Glacial Acetic Acid* contains 99 per cent. *Dilute Acetic Acid* contains 6 per cent, about the same concentration as vinegar (Acetum). Its dose is 2 to 4 cc., 30 to 60 minims.

FORMATES

Local Action.—Free formic acid occurs in several animals (ants and so forth, Faust, 1910) and plants (nettles), and is partly responsible for their irritant effects. (Berchart, 1915, concluded that the effects of nettles are not due to formic acid.) Formic acid resembles acetic acid, but is more volatile, more irritant, more antiseptic and more resistant to oxidation. It has a popular reputation as a counterirritant, but is probably not superior to other irritants. It is usually employed in the form of *Spiritus Formicarum,* corresponding to 1 per cent of the absolute acid in two-thirds alcohol (this was formerly obtained by macerating ants).

On oral administration, formic acid behaves almost quantitatively like acetic acid. Water containing 0.25 per cent of either formic or acetic acid, administered to rats for many weeks, in daily dosage up to 0.2 cc. of acid per Kg. of body weight (equivalent, in man, to 6 liters of 0.2 per cent acid per day), produced no effects whatever; not even diuresis. Twice this dosage interfered materially and progressively with growth and appetite, both acids again behaving alike (Sollmann, 1921).

Formates by Mouth.—The toxicity is low, so that 6 to 10 Gm. of sodium formate may be taken daily for some time (Fleig). Eppinger, 1913, administered sodium formate, 3 to 4 Gm. daily, to three patients. Two felt no discomfort; the other developed albuminuria and hematuria, persisting for five days; but this must have been a coincidence.

Action after Absorption.—The formates act practically as indifferent salts. The general circulation is not affected by large doses. Enormous doses depress the heart (Livierato, 1906). They are said to produce methemoglobinuria (Croner and Seligmann, 1907). Diuresis may result (Fleig), doubtless owing to simple salt action. Stimulant effects of various kinds have been claimed, but shown to be absent (Fleig, 1907, literature).

Therapeutic Uses.—Formates were exploited rather fantastically as an elixir of youth, destined to confer on man the vigor and indefatigability of insects; and to cure various ailments, mainly of the neurasthenic type (H. Stern, 1906). Fleig exposed the uncritical nature of the evidence and showed that the results were due solely to suggestion.

Fate.—Formates are oxidized less readily than acetates, so that a greater proportion (up to two-thirds) appears unchanged in the urine. With smaller doses, the destruction may be more complete (Pohl). The oxidation occurs mainly in the liver (Fleig, 1907).

Normal Occurrence.—A small quantity of formate occurs normally in mammalian tissues. In man, the normal daily urinary excretion is 13 to 120 mg. This indicates that considerable quantities are formed in intermediate metabolism, probably of all classes of foods. It is also formed from formaldehyde and methyl alcohol, but not from ethyl alcohol (Dakin, Janney and Wakeman, 1913).

Acid formicum, as official in foreign countries, contains 25 per cent of HCO_2H. The dose is stated as 1 to 20 drops.

Allyl formate and other allyl compounds act similarly to monoiodoacetate by interfering with the breakdown of carbohydrate, in yeast, frog skin, and liver tissue (A Fleckenstein, 1944). In rats, intraperitoneal injection injures the sinusoidal capillaries of the liver and produces hydropic degeneration and necrobiosis of the hepatic cells, and hemorrhages into periportal areas (A. Rosin and Doljanski, 1946).

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SUCCINATES

Sodium succinate can be used for clinical alkalinization of urine. It is reported as effective as acetate or citrate, and better tolerated (Becker-Freyseng and Liebich, 1938).

Analeptic.—Intravenous injection of sodium succinate is reported to awaken patients from narcotic sleep; see under Barbiturates.

Leukocytes.—Hypodermic injection of 0.1 cc. of 1 per cent sodium succinate in man is said to increase the leukocyte count of the blood by 20 to 70 per cent (Hammett *et al.*, 1917).

Heart.—Direct application of concentrated solutions depresses the heart, similarly to tartrates (Salant and Livingston, 1917).

LACTATES

These are but slowly absorbed and therefore act as saline cathartics. They are completely burned in the organism and have no other action (Faust, 1910). It has been claimed that lactates somewhat limit nitrogen metabolism, after the manner of fats. Lactic acid is an important link in the energy metabolism and rigor mortis of muscle and other tissues. It is formed in the brain after decapitation, more rapidly than in any other tissue (McGinty, 1925). Various preparations of lactic acid administered by mouth or hypodermically have a slight inhibiting effect on transplanted *mouse sarcoma,* probably by disturbing the metabolism of the animals (Parfentjev *et al.*, 1934).

It should be remembered that lactic acid is a strong, corrosive acid. Several infants have died from milk acidified with supposedly 0.8 per cent lactic acid (E. G. Young and Smith, 1944).

Sodium r-lactate, N.N.R., is used for the treatment of acidosis by intravenous or hypodermic injection of one-sixth molar solution (1.87 per cent W/V, approximately isotonic with blood). The rate of injection should usually not exceed 300 cc. per hour. *Sodium Lactate Injection*, U.S.P., is to be made with water for injection, the concentration to be specified. *Lactate Ringer solutions* are also used.

MALATES

These are largely destroyed, even on hypodermic administration, but from 3 to 40 per cent escapes into the urine. They produce much less damage than tartrates or citrates (Wise, 1916).

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CITRATES

These are used chiefly as alkaline diuretics, and in blood transfusion. Citric acid (about 1 per cent) is employed as a refrigerant drink in fevers, often as lemonade.

Fruit Acids.—The acidity of fruits is due mainly to citric acid; other acids occur only in small quantities. Tartrates are important only in grapes (Bigelow and Dunbar, 1917). *Lemon juice* contains about 8 per cent of citric acid, a large lemon about 4 Gm., ordinary lemonade about 0.5 per cent. Oranges contain sufficient base so that the drinking of *orange juice* turns the urine alkaline; the oxidation is complete even when large quantities are taken, *i. e.*, 2400 cc., containing about 48 Gm. of acid, in a day (Blatherwick and Long, 1922).

Routine use of lemon juice in water dissolves dental enamel (E. C. Staine and Lovestedt, 1947).

Fate and Use as Antacid.—Citrate is rapidly absorbed and completely and quickly oxidized in the body or transformed into liver glycogen (C. A. Kuether and Smith, 1941). After oral administration, less than 1 per cent is excreted unchanged by the urine. Large doses of sodium citrate (30 to 50 Gm. per day) can be administered clinically for alkaline diuresis without digestive disturbance (Lichtwitz, 1911).

In normal individuals, the *change of acid:base balance* after ingestion of 6 to 12 Gm. of sodium citrate or its equivalent of sodium bicarbonate (4.5 to 9 Gm.) is neither prolonged nor marked. After 20 Gm., the change is maximal one and one-half to two hours after administration (Cape, 1935). With *oral administration* of sodium citrate, 0.2 to 2 Gm. per Kg., the rise of citrate concentration in the blood lasts three and one-half to seven and one-half hours. An average of 0.7 per cent escapes oxidation and is excreted in the urine; no extra citrate appears in the feces. The addition of free citric acid to a constant diet does not affect the *p*H of the urine (C. C. Sherman, Mendel and Smith, 1936). When *injected into a vein*, the citrate disappears rapidly from the circulation. None escapes into the urine with intravenous injection, up to 0.5 Gm. per Kg. After *hypodermic injection* in rabbits, about 12 per cent is excreted in the urine; with cats, 30 per cent; with dogs, 40 per cent (Salant and Wise, 1916).

Normal Occurrence.—Human and dog's urine, blood and other body fluids constantly contain small amounts of citrates, which are probably synthesized as well as oxidized in normal metabolism (C. C. Sherman, Mendel and Smith, 1936). The normal human *urinary excretion* is about 0.5 Gm. daily (Amberg and McClure, 1917); the level in *blood serum* is normally about 2.5 mg. per 100 cc., with a range of 1.5 to 5 mg. in pathological conditions, the highest values in hepatitis (Thunberg, 1933). Its concentration in *body fluids* is between 20 and 200 mg. per cent; in *soft tissues*, 0.1 to 0.2 mg. per cent (A. H. Smith and Orten, 1937). Human *prostatic fluid* contains 0.5 to 2.5 per cent (C. Huggins and Neal, 1942). The *skeleton* contains 70 per cent of the total citrate of the body, more than one per cent of the mineral matter, presumably in combination with calcium (F. Dickens, 1941). Human and dogs' *teeth* contain somewhat over 0.5 per cent of their dry weight, the dentine having five to eight times the concentration of the enamel (A. H. Free, 1943). The urinary output is increased by alkalis (Kuyper and Mattill, 1933); in dogs up to a hundred times the normal (Sherman *et al.*, 1936). Changes of calcium excretion induced by diet or parathyroid deficiency produce parallel changes in the urinary citrate (E. Shorr, Almy *et al.*, 1942). Conversely, hypodermic injection of sodium citrate into dogs causes prompt and considerable increase of urinary calcium excretion, the blood calcium level being practically unaffected. Repeated injections into puppies or young rats result in bone changes similar to those caused by large doses of parathormone (G. Gomori and Gulyas, 1944).

Disionization of Calcium.—Citrates form double salts with calcium which do not liberate calcium ions, as judged by their chemical behavior (Sabbatani, 1901), conductivity measurements (Shear and Kramer, 1928) and pharmacologic tests such as the frog heart (Hastings, McLean *et al.*, 1934). With *p*H 7.7, a part exists as $CaCi^-$ anion (Mg and Sr behave similarly). Citrate makes the entire serum calcium ultrafiltrable, presumably by taking it away from protein. Lactate and acetate do not affect the normal nonfiltrable calcium ratio of 45 to 47 per cent, in rabbits (Shelling and Maslow, 1928).

Serum Calcium and Phosphate Level.—Intravenous injection of sodium citrate into normal dogs causes an immediate fall of Ca, although less than with oxalate. It recovers rapidly and completely in a few hours. The phosphate is slightly lowered during the Ca fall, and rises markedly during the Ca recovery. The recovery is attributed to mobilization of bone Ca and PO_4, apparently by mediation of the parathyroids, for after excision of these, the recovery is much slower (Tsai and Hsu, 1930).

Coagulability of the Blood.—Citrates, like other Ca inactivators, render the blood noncoagulable *in vitro*. The addition of 0.2 per cent of citrate to shed blood prevents coagulation completely, even for forty-eight hours; 0.1 per cent does not hinder it at all. One per cent of citrate (1 cc. of 10 per cent citrate per 10 cc. of blood) keeps the blood noncoagulable for two weeks, but shrinks and injures the corpuscles.

Intravenous injection of sodium citrate has the opposite effect: it shortens the coagulation time. This occurs in human subjects with 10 to 50 cc. of 10 per cent citrate (Weil, 1915), returning to normal within twenty-four hours (Lewisohn, 1917). It has been attributed to injury of the platelets, leading to liberation of the thromboplastin (N. Rosenthal and Baehr, 1922).

With intramuscular injection, the effect depends on the dose, the coagulability being increased by relatively small doses (0.125 Gm. per Kg.) and diminished by large doses (De Souza and Hocking, 1935). In *hemophilia*, intravenous injection produces an immediate and marked shortening of the coagulation time. This is followed in one to two days by return to the original or even to slower coagulation. Intramuscular injection has no effect (Ottenberg, 1916).

Use in Transfusion.—Weil, 1915, introduced the use of "citrated blood," the blood of the donor being kept uncoagulated by the addition of sodium citrate. This may be injected at once, or preserved for a time. Wassermann, agglutination, hemolysis and other tests must be made as usual. *Citrated normal human plasma*, U. S. P., contains 0.4 per cent.

Dosage.—Lewisohn, 1915, 1917, advised 0.25 per cent of sodium citrate. The total injection should not exceed 1200 cc., corresponding to 4.8 Gm., or toxic citrate effects may ensue (A. C. Ivy, Greenzard *et al.*, 1943; J. Bruneau and Graham, 1943).

"Reactions" Following the Transfusions of Citrated Blood.—Citrated-blood transfusions are sometimes followed by a fairly severe chill and fever of about 2.5° F., in half an hour, returning to normal in four to eight hours. This reaction has little practical importance, and is apparently due to alterations produced in the corpuscles (Drinker and Brittingham, 1918).

Other Anticoagulants.—In laboratory experiments, the coagulability of blood can easily be diminished or abolished. Leech extract, heparin and certain azo dyes have this effect, whether they are injected or added to shed blood; albumoses, only when injected; citrates, hexametaphosphate, oxalates, fluorides, concentrated solution of other salts and urea, formaldehyde, hydrocyanic acid, and so on, only on shed blood (by removing the calcium or inhibiting the fibrin ferments).

Other actions of citrate on intravenous injection or excised organs (not with oral administration) correspond to calcium deprivation (Sabbatani, 1901; Vietinghoff-Scheel, 1902; Martin, 1904; Gordonoff *et al.*, 1930).

The *intravenous toxicity* varies with the rate of injection. The oral toxicity is low (Salant and Wise, 1916). The injection of minute quantities into the *brain* produces convulsant effects. Repeated hypodermic injections of increasing doses create considerable *tolerance* (Robertson and Burnett, 1912).

Effects on Circulation.—As used clinically, this is practically unaffected. Larger doses, 30 mg. of sodium citrate per Kg., depress the heart muscle and stimulate the vasomotor center in dogs. The renal vessels may be dilated (G. R. Love, 1923). Citrate lowers the threshold of ventricular fibrillation by galvanic stimulation (A. G. Rojas *et al.*, 1942). The *cardiac vagus* is completely paralyzed by intravenous injection of sodium citrate, in cats and in turtles, probably between the pre- and postganglionic fibers. Oxalate produces the same effect. It is apparently due to lowering of the calcium ion concentration, and may be prevented by injection of calcium chloride. Spontaneous recovery is complete in twenty to thirty minutes in cats (G. D. Shafer and Crismon, 1936).

Excised Intestines.—Strong solutions depress all portions of the intestines of rabbits; weaker concentrations stimulate the small and depress the large. With cats, the small and large intestines are both depressed (Salant and Schwartze, 1917). When injected intravenously into dogs, small doses of sodium citrate stimulate the gastric and intestinal movements feebly. Larger doses, 100 mg. per Kg., rapidly injected cause a temporary depression of the stomach and intestines, and a sympathetic stimulation similar to epinephrine (G. R. Love, 1923). *Excised uterus* of guinea pigs, virgin or pregnant, respond with marked increase of tonus to the addition of 0.00015 to 0.0009 per cent, with decreased tonus above 0.001 per cent (Messini, 1929).

Coagulation of Milk.—The inactivation of calcium by citrates prevents the clotting of milk. Their addition to cows' milk produces a looser curd in the stomach. This is utilized in infants (1 to 3 grains of citrate per ounce of milk), when ordinary milk is not well borne (curds in vomitus and stools). It should be reduced or omitted as soon as the need is passed (Cotton, 1906; R. Curtis, 1916).

PREPARATIONS.—***Sodium Citrate, U.S.P.**; $Na_3C_6H_5O_7\cdot 2H_2O$; a white granular powder; odorless; cooling saline taste. Efflorescent. Freely sol. in water (1:1.5); insol. in alc. Dose, 1 to 4 Gm., 15 to 60 grains. *Anticoagulant Sodium Citrate Solution*, U.S.P., contains 2.5 per cent of the official citrate in 0.9 per cent solution of sodium chloride. It is available as (1) nonsterile; (2) sterile not for parenteral use; and (3) for parenteral use. The last (in water for injection) is dispensed unless the others are specified. *Anticoagulant Acid Sodium Citrate and Dextrose Solution*, U.S.P. ("ACD Solution"), contains sodium citrate, U.S.P., 2.2; citric acid, 0.8; dextrose, 2.45, in 100 cc. of water for injection. *Potassium Citrate*, U.S.P., has similar properties. *Effervescent Potassium Citrate*, U.S.P., contains 20 per cent of potassium citrate, with sodium bicarbonate and tartaric and citric acid; average dose, 4 Gm., 1 drachm. *Citric Acid*, U.S.P., $C_3H_4(OH)(COOH)_3\ H_2O$, is a tribasic organic acid obtained from the juice of limes or lemons. Colorless, translucent prisms or a white powder; odorless; having an acid taste:

efflorescent in warm air. Very sol. in water (1:0.5); freely sol. in alc. (1:1.8). Dose, 0.3 to 2 Gm. *Citric Acid Syrup,* U.S.P., containing 1 per cent of citric acid and 1 per cent of Lemon Tincture, is used as flavored vehicle.

Propionate of sodium, $CH_3.CH_2.COONa$, or of calcium, which is used under the trade name "Mycoban", to inhibit the growth of molds in dough and dairy products, has been found effective clinically against superficial fungus infections, ringworm and thrush; it is also effective against bacteria. It may be used as a dusting powder (10 per cent, with talcum) or as 10 per cent ointment (E. L. Keeney *et al.*, 1944).

Undecylenic acid, $CH_3.C_2H_2.C_7H_{14}.COOH$, appears to be even more effective. A. L. Shapiro and Rothman, 1945, recommend 5 per cent of the acid and 20 per cent of zinc undecylanate in a vanishing cream base. This does not irritate inflamed lesions.

M. B. Sulzberger and Kanof, 1947, who compared the prophylactic and treatment value of nine formulas against dermatophytosis in the Navy, found undecenylate somewhat superior; propionate ranked fifth, a boric-salicylic powder seventh; but the differences were not great.

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URATE SOLVENTS

Acid urates occur in solution in the blood and tissues; and as the peculiar sodium biurate deposits in gouty tophi. In the urine, acid urates also occur in solution. When the urine is scanty or acid, they may be deposited as free uric acid or "quadriurate"; *i. e.*, a mixture or compound of free uric acid and acid urate. These deposits may concrete into urinary calculi. Once formed, they are difficult to redissolve by restoring the reaction, unless this is strongly alkaline. It is impossible to do this in the tissues; it is doubtful even for the urine, but in this, further urate precipitation can be prevented by dilution and moderate alkalinization (Buchheim, 1853), taking care that the latter does not lead to the precipitation of phosphates which might be deposited on the calculus. It has been attempted to dissolve the urate by the administration of lithium and particularly diethylene diamine (piperazine) and related organic bases, which form relatively soluble urates in pure solution, but these bases have no material advantage; in the presence of excess sodium, the less soluble salt is formed. Deposition of urates in the tissues is not affected by alkalis (Ritter) since these do not change the *p*H of the tissue fluids. The urate level of the blood may be diminished somewhat by liberal diuresis, and more effectively by salicylates and cinchophen, which lower the renal threshold for urates, and this may perhaps diminish somewhat the tendency to the formation of tophi, but it does not redissolve those already deposited.

Salts of Uric Acid.—*Uric Acid,* $C_5H_4N_4O_3$, is a weak dibasic acid, which under proper conditions can form three series of salts, namely: *Neutral urates,* $C_5H_2N_4O_3Na_2$; also called dibasic, normal or secondary urates. These are formed only by strong alkalis, and cannot occur under natural conditions, being decomposed by CO_2 and even water. They need not be considered further. *Acid urates,* $C_5H_3N_4O_3Na$; also named monobasic or primary urate or biurates. They are neutral to litmus. *Quadriurate,* $C_5H_3N_4O_3Na + C_2H_4N_4O_3$; also named hemibasic urates or tetraurate. It is a mixture or solution of uric acid and acid urate. The quadriurate forms the sedimentum lateritium in cooling acid urines. On standing, it separates uric acid crystals. Water dissolves out the acid urate and leaves the uric acid. *Other urate deposits in urine* may consist of uric acid in acid urines; of acid urates in acid or neutral urines; and ammonium urate in neutral or ammoniacal urine. The acid urate is generally amorphous, but may be crystalline in neutral urine. The consolidation of urinary precipitates into *urinary calculi* involves the cooperation of a "colloidal mortar," presumably fibrin (H. Schade). *Urate tophi* consist always of acid urates (Ritter, 1897); so do the uratic deposits in animals, even when free uric acid is injected (Loghem, 1907).

Solubility and Precipitation.—Free uric acid is very little soluble. The acid urates also have a limited solubility. They behave as colloids, and their solution may be favored or hindered by a variety of conditions, some little understood.

The study of the solubilities is complicated by the small quantities going into solution, the polyvalence, formation of colloidal solutions, supersaturation, the influence of small quantities of impurities, decompositions, and so forth (His and Paul, 1900). Pure water dissolves at 18° C. only 25 mg. of uric acid per liter = 1:40,000 (His and Paul). At 40° the solubility is probably doubled. *Alkalis,* even the bicarbonate or phosphate, transform part of the uric acid into acid urate, and therefore increase its solubility. *Free acids* diminish the solubility, since they decrease the ionization; undissociated uric acid is less soluble (His and Paul). Haskins, 1916, found that the solvent power of *urine* for uric acid varies with its reaction and concentration. Urines of *p*H = 6.1 or less cannot dissolve any added uric acid; those that are less acid take up more according to their alkalinity. Concentrated urines dissolve more (though not in strict proportion) than do dilute urines of the same reaction. The acid NaH_2PO_4 liberates and precipitates uric acid; this is counteracted by the presence of the alkaline Na_2HPO_4; but excess of the latter precipitates the acid urate by "salting out" (Ritter). Addition of free uric acid to urine may precipitate a part of the uric acid originally in solution (Voit), presumably by acting as a crystallizing nucleus. The solubility in *serum* is much greater (500 mg. per liter) than in water (Bechold and Ziegler, 1909). This is probably due to the *colloids,* and it is likely that the colloid constituents of the urine also contribute to the solubility of the uric acid and urates (Lichtwitz, 1910). Ruedel, 1892, claimed that *urea* has an important solvent action, but Ritter, 1897, found this limited. O. S. Gibbs, 1929, adduced evidence that fowls' blood contains a specially soluble form of uric acid.

Uric acid excretion occurs almost exclusively by the urine. The *normal threshold* is lowered by cinchophen and salicylates, and by water or saline diuresis (J. H. Robertson, 1914; J. L. Morris and Rees, 1923). Strenuous exercise and ingestion of lactic acid decrease the output (Quick, 1935). Injection of uricase into hens lowers the uric acid concentration of their blood sharply (E. H. Oppenheimer, 1941). *Methenamine* and the related compounds (Citarin, and so forth) have a solvent and destructive action on uric acid, even in acid urines (Stevens and May, 1911; Haskins, 1915). This is due to their formaldehyde. They were therefore advocated as urate solvents. The action, however, is imperceptible with the ordinary doses (review, Hanzlik, 1916).

Intravenously injected uric acid remains in the blood of gouty patients longer than with the nongouty (McClure and Pratt, 1917). It disappears promptly from the blood of dogs and rabbits and is at first fixed almost exclusively in the kidneys, but these return to normal in a few hours. The amount eliminated by the urine is but little increased. The ultimate fate is not known (Bergami, 1930). In fowls, the injected urate is promptly excreted completely, and even lowers the urate level of the blood (Gibbs, 1929).

Actions of Urates.—The importance of these lies in the fact that they may be formed or retained in excessive amounts in pathologic conditions, when they first produce inflammatory necrosis of cells, and are then deposited in insoluble granular form. This, becoming crystalline, acts as a mechanical irritant, producing the phenomena of gout. These can be stimulated in animals by the injection of suspensions of acid sodium urate, and in birds by the subcutaneous injection of chromates, or even by ligation of the ureters. The cause of the abnormal appearance of the uratic deposits in gout and similar conditions is not understood.

Relation of Uric Acid to Gout.—The occurrence of urate tophi is a striking proof of disturbed uric acid conditions in this disease. The uric acid of the blood is generally increased. It was formerly believed that definite changes in the uric acid content of the blood occurred during the acute gouty attacks, but modern results indicate that the urate concentration is the same during as between attacks. Attacks occur also when the urate concentration has been lowered by cinchophen (Daniels and McCrudden, 1915). The urate deposits are not due to simple oversaturation, for the solvent power of serum for uric acid is much higher than the concentration in gout. Presumably it is caused by alterations, local or general, of the colloidal equilibrium (Lumiere).

Piperazine, diethylene-diamine, $NH(CH_2)_4NH$, produces no symptoms and is practically nontoxic. The solvent power for uric acid, in pure solution, is higher than that of Li_2CO_3 (Stevens and May, 1911), but still insufficient to make much impression on a urate stone (Penzoldt). In the presence of Na salts, and therefore in the blood and urine, it is not superior to other alkalis (Meisels, 1893); and since a part is oxidized, and therefore only a fraction appears in the urine, its solvent power is less than that of $NaHCO_3$ (Haskins, 1916). These limitations apply also to the derivatives of piperidine (dimethylpiperazine = *Lycetol,* Wittzack, 1894; ethylene-ethenyldiamine = *Lysidine.* Ladenburg, 1894). Eczema has been reported from lysidine (Ortner). *Piperidine,* $CH_2(CH_2)_4NH$, was introduced as urate solvent by Tunnicliffe and Rosenheim. The dose of the bitartrate is 0.6 to 1 Gm. three times daily. Its pharmacologic effects resemble those of coniine (C. R. Linegar *et al.,* 1943).

METALS AND THEIR COMPOUNDS

The various metals and their compounds have many pharmacological features in common. Their salts combine with proteins, and therefore act locally as astringents, irritants, corrosives and antiseptics. Their absorption, storage and excretion are similar. After absorption, their effects are chiefly on the capillaries, analogous to inflammation, resulting in collapse, enteritis, colitis, nephritis and sometimes hepatitis. With continued exposure, the effects are cumulative and result in chronic poisoning, chiefly nutritional and nervous, peripheral and central. Many metals stimulate the bone marrow and mobilize the reticulocytes; large doses become toxic and produce anemia. Iron is an indispensable component of hemoglobin, and traces of some other metals (copper, manganese, zinc) promote growth and are probably also indispensable; aluminum and nickel are apparently not needed (Sharpless, 1933). The activity of metal compounds depends on their *solubility,* and their systemic action on their absorbability, which varies greatly. Compounds insoluble in water may undergo chemical changes in the intestinal tract or in the subcutaneous tissue which render them soluble and absorbable. The free metals rarely if ever act directly, but only after being transformed into compounds. Most of the soluble metal compounds may be arranged into the following *groups:* (1) *Ionizable salts,* such as ferric chloride, generally precipitate proteins and therefore have marked local actions. They circulate in the blood, probably as protein salts, and produce the typical actions of each metal. (2) *Double salts,* such as iron and ammonium citrate, contain the metal as part of a complex anion (ferrocitrate), which do not precipitate proteins directly, and therefore have but little local action. They generally split off some metal cations, however, and therefore eventually produce the systemic actions of the ionizable compounds. (3) *Molecular compounds,* where the metal forms an integral part of a nonionizable molecule. These may have direct actions that differ materially from those of the ionizable compounds, as the iron in hemoglobin; or they may break up fairly readily and form ionizable compounds, as with cacodylic acid. *Metal alkyls,* which belong in this group, act first as aliphatic narcotics, then as molecular compounds, and finally, after decomposition, they produce the ionized metal effects. They penetrate into living cells much more easily than ready-ionized compounds (Sollmann and Seifter, 1939). (4) *Colloidal metals and metallic oxides and salts* have but little action directly, but because of their large surface they are fairly readily converted into ionizable salts. Their direct injection into the blood stream provokes colloidoclastic reactions, and they are taken up by the reticular endothelium.

The action of metals on cells occurs in two stages (Euler and Waller, 1924): (1) rapid adsorption on the surface, reversible by hydrogen sulfide; (2) slow penetration, producing irreversible effects. The *local actions of metallic salts,* as also their direct antiseptic action, were discussed under *Local Irritants and Astringents.*

Habituation to the Local Action.—If the administration of a metallic salt is begun with small doses and gradually increased, it may become possible to administer without local effect doses which would at first have produced corrosion (Hausmann, 1906). Habituation diminishes the absorption of arsenic, but not of antimony (Cloetta, 1906, 1911). *Lower organisms,* yeasts, bacteria and protozoa, acquire considerable tolerance to the various metals. This may be transmitted for generations, and may or may not extend to other metals (infusoria, Neuhaus, 1910; trypanosomes, Ehrlich, 1910).

Absorbability of the Metals.—Arsenic, mercury and uranium are the only metals whose ordinary salts are absorbed sufficiently to cause acute systemic poisoning with noncorrosive doses. Phosphorus, which behaves pharmacologically in many respects like metals, is absorbed still more readily. Other metals are absorbed much more slowly. To this class belong lead, silver, tin and iron. Metallic poisons are generally more toxic to herbivora than to carnivora, probably because they remain longer in the alimentary canal of herbivorous animals, allowing greater absorption. Any metallic salt, if given in strong solution, will cause *corrosion* of the mucous membrane of the alimentary canal and will then be absorbed, and would exert its systemic action were it not that the local effects often kill before the systemic can come into play. Lead, copper and zinc oleates are said to be *absorbable through the skin* (C. Voegt and Burchardt, 1916). This holds also for mercury oleate.

The **excretion** of metals occurs mainly by the urine and feces. The urinary excretion is generally the greater, perhaps by five to ten times, and the concentration in the urine averages about ten times that of the blood. The urinary output reflects at least the direction and very roughly the quantity of the blood concentration. The fecal excretion is more complex and less proportionate. It occurs chiefly by the bile, but in part directly into the intestines, probably by the histiocytes. With oral administration the feces may contain large amounts of the unabsorbed compounds. Traces may continue in the excretions by mobilization from the tissues, long after the administration has been discontinued.

Distribution and Retention of Metals.—The ingested or injected metal compounds leave the blood rapidly for the tissues, which soon have the higher concentration. A part is excreted, promptly or more often slowly, according to the compound used; the greater part of the metal is generally retained in the tissues for a long time, at first particularly in the reticulo-endothelial system, later in the interstitial tissue, partly as visible granules (as in hemochromatosis, argyria, chrysiasis, and so forth), often persisting through life; part also is in diffuse form, probably in the tissue cells. Lead and some other metals are stored in the bony trabeculae, analogous to calcium. With oral and intramuscular administration, the chief deposits are in the liver and kidneys; with intravenous injection the lung and spleen may be relatively richer for a few hours, by straining off the flocculates. Other organs contain considerably less, but generally more than the blood. The relative concentration in the kidneys and liver varies reciprocally for different metals, as shown in the following series,

higher in kidney: *higher in liver:*

$$\Lsh \text{U} \leftarrow \text{Au} \leftarrow \text{Bi} \leftarrow \text{Hg} \leftarrow \text{Pb} \rightarrow \text{As}^{\text{V}} \rightarrow \text{Th} \rightarrow \text{As}^{\text{III}} \rightarrow \text{Ag} \rightarrow \text{Cu} \Rsh$$

(Hevesy and Wagner, 1930). The explanation of this selectivity is not known; the local acidity is concerned in colloidal silver (Koller-Aeby and Koller, 1930). *Phosphatase* may be another factor, since metal phosphates precipitate rather easily, especially in the kidneys, as well as in the bones. When the metals are first absorbed into the blood stream, they must be ionizable, at least in part, since sulfides are precipitated in the mucous membrane of the mouth and colon. When they enter the tissues, however, they become insoluble, physiologically inactive, and difficult to mobilize. The therapeutic and injurious effects are probably determined in the short time when effective concentrations of the metal ions are circulating in the blood. The delayed effects may be conceived as later consequences of the primary injury, and the cumulative actions are probably the gradual summation of successive toxic injuries.

The **acute effects of metal compounds** are dominated by the local actions of the ionizable salts, based on protein precipitation, resulting in irritation on oral or hypodermic injection, and intravascular precipitation or flocculation on intravenous injection. The slow absorption of most metallic compounds adds to the difficulty of observing acute systemic effects. Molecular compounds devoid of these objections act primarily as molecules rather than as the metal.

Intravenous injection of dissociable metal compounds generally causes colloidoclastic shock, with sharp or slow fall of blood pressure, in proportion to the mutual precipitation of the compound and of blood protein. The more manageable colloidal metals, and some molecular compounds such as mercurochrome and flumerin, have been used to produce "nonspecific" reactions to combat septicemia, sometimes with good and often with bad results. A milder degree of this action constitutes the "nitritoid crises" such as occur with arsphenamine injections.

Acute systemic effects from easily absorbable metallic salts are seen with arsenic, mercury and uranium. They involve chiefly injury to the capillary endothelium, especially of the abdominal viscera, resulting in acute enteritis, with shock and dehydration, even on parenteral administration; colitis, nephritis and sometimes hepatitis. It appears probable that all the damage is done soon after absorption, and that the later phenomena are the consequences of this early injury.

The actions of arsenic, mercury and probably of most metals appear to be concerned with the *-SH groups* that are essential to cellular metabolism. Metal actions also combine with the *carboxyl groups* of amino acids and therefore render proteins more basic.

The capillary injury varies at least in degree for different metals, and it has been suggested, probably too schematically, that these may be divided into *two groups;* the first group acting mainly peripherally on the *blood vessels,* and the second group acting peripherally on the *heart.* To the first group belong arsenic, antimony, uranium, bismuth, iron, magnanese, selenium, tellurium, aluminum, tin, nickel, cobalt, gold and platinum (Wohlwill, 1907); to the second group, lead, phosphorus, copper, zinc, cadmium, mercury, vanadium, cerium and thallium. In the *perfused heart,* all metals (in the form of lactates) produce block and diastolic standstill (Voegtlin, 1915).

Metal nephritis begins usually in the epithelium of the convoluted tubules and spreads to the glomeruli. If the poisoning is chronic, the nephritis may become interstitial and lead to renal cirrhosis.

Nephritis has been described in poisoning by the following metals: Ag, Al, As, Au, Be, Bi, Cd, Ce, Co, Cr, Cu, Hg, Mn, Ni, P, Pb, Sb, U, W, Zn. There may also be renal *glycosuria, i. e.,* the appearance of sugar in the urine without hyperglycemia (Luzzato, 1914). *Tissue cultures of renal epithelium* are especially sensitive to Pb and Cu; of *liver cells* to Zn, Co and Ni (Samnié and Verne, 1934).

Subacute metal poisoning develops from the acute, if this is not quickly fatal, since the consequences of the capillary and tissue injury progress for a time. Indeed, with nonprecipitant compounds symptoms may be delayed for several days, when the metal may have disappeared from the blood (White, 1880). Tartar emetic, when injected in appropriate doses into a vein, disappears from the blood in ten minutes, but the first symptoms may be seen only after some twelve hours.

Chronic metal poisoning may develop from subacute, but commonly involves repeated or continued exposure with cumulation of injury. The phenomena take chiefly two directions: nutritional—digestive disturbances, anemia, cachexia, nephritis; and *nervous,* functional and anatomical, peripheral and central lesions, neuritis with tremors and paralyses, encephalopathia, vasomotor disturbances, colic, arthritis and gout. The two groups interlock, in that the nutritional disturbances tend toward neuritis, and conversely.

The *digestive disturbances* are among the earliest indications of chronic metal poisoning. Small doses of practically all metals produce more or less hyperplasia of the bone marrow and increased *hematopoiesis;* large doses cause injurious irritation, anemia and toxic mobilization of immature erythrocytes. Iron is an indispensable constituent of hemoglobin. Its utilization is aided by small doses of other metals: Cu, Co, Mn, Ge, As and even Hg. Traces of Cu, Mn and Zn promote *nutrition* and growth, and are probably essential.

Stomatitis occurs in chronic poisoning by mercury, bismuth and lead. It is due to the formation of the irritant and toxic sulfides of these metals with the products of bacterial putrefaction, in a vicious circle. The local effects of these sulfides depend partly on their different solubilities (Santesson, 1934).

The *reaction of living bone to various metals and alloys* was investigated by H. A. Davenport and Bothe, 1941. Copper produces local necrosis; Ti, Pb, Cr, Al, vitallium and stainless steel are well tolerated.

Colloid metals may be obtained by establishing an electric arc between metallic wires under water, or by the action of reducing agents on solutions of metallic salts. These can be made into more concentrated solutions (Voigt, 1914). Colloid solutions of Pt, Ag, Hg, Au, Bi, Cd and Ir, and also of their insoluble oxides and salts, have been prepared by these methods. Colloid solutions do not produce the ion actions of the metals directly. The colloid condition, however, gives them *catalytic properties; i. e.,* minute quantities may induce reactions in large quantities of other substances (*e. g.,* conversion of alcohol into acetic acid), the metal taking no part in this transformation. This catalysis is hindered by many poisons. The metals *pass readily from the colloid into the ionic condition, e. g.,* by the action of bacteria, and may then exert the ordinary action of the metals. Since this conversion occurs but slowly, these actions are mainly local and produce a minimum of irritation. After intramuscular or peritoneal injection, the *absorption* is slow, and not exclusively by the leukocytes (Voigt, 1916). If injected intravenously, they sojourn only a few minutes in the blood (Niculescu, 1912), and are then deposited, especially in the liver and the hemopoietic and excretory organs (Voigt, 1914, 1916).

Protein Stabilizers.—Colloidal metals for clinical use (for instance Collargol) are often "stabilized" by the addition of proteins. These may produce active or passive anaphylaxis (Hanzlik and Karsner, 1920), and are at least partly responsible for the therapeutic and toxic "reactions."

Pharmacologic Actions of Colloid Metals.—Their gradual transformation into the ionized form eventually produces the ordinary systemic effects of metals. They have been used, hypodermically and intravenously, for this purpose, without serious advantage. (Solutions should not be made isotonic with salt, since electrolytes cause precipitation.) They also produce other rather indefinite and inconstant effects, probably attributable to the colloid condition: hyperpyrexia, first hypo-, then hyperleukocytosis, renal and intestinal irritation, and fatal coma (Gros and O'Connor, 1911). They may be followed by increased excretion of nitrogen and uric acid (Ascoli and Izar, 1907). Repeated intravenous injections of colloid metals or of other foreign colloids produce marked irritation of the lymphoblastic tissue of the spleen, lymph glands and bone marrow (Nissen, 1922). An interesting effect has been described by Gaudrelet: in a normal animal, the intravenous injection of the dye thionin has little effect, but it exaggerates the hypotensive effect of nigrosin injection. This response fails to occur in animals injected with electrocolloid metals, peptone or other colloids.

Therapeutic Use Against Infections.—Colloid silver was extravagantly lauded as an internal antiseptic in puerperal and other septicemias and infections; but the claims do not stand critical examination (Report, Council on Pharmacology and Chemistry, 1909). Gros and O'Connor found that colloid metals, like charcoal, adsorb poisons, alkaloidal as well as toxins, and therefore decrease their toxicity, but the decrease is insignificant and does not occur at all unless the poison was treated before being injected. Phagocytosis is perhaps somewhat increased for some bacteria, but not for all (Le Fèvre de Arric, 1913). Colloid silver or mercury is fairly antiseptic, but not germicidal (Marshall and Killoh, 1915).

Dangers.—Colloid silver preparations are likely to deteriorate into the insoluble form and may thus produce embolism (H. J. Hamburger, 1909). A number of deaths have occurred probably by vascular embolism from the injection of collargol into the renal pelvis for x-ray diagnosis (Eisendrath, 1914). Buerger, 1914, found that these injections may penetrate the renal parenchyma to the surface of the kidney, and lead to necrotic and suppurative foci.

Metal chemotherapy of cancer started with the announcement of Wassermann, Keysser and Wassermann, 1911, that they had succeeded in causing the disappearance of rat tumors by the intravenous injection of selenium eosin compounds. Since then, similar favorable results were reported for colloidal copper, platinum, sulfur and some other colloids and organic metal compounds (L. Loeb and co-workers, 1912 to 1913). Even human tumors seemed to show some retrogression. Uhlenhuth, 1912, and Walker, 1912, failed to confirm the animal experiments with eosin selenium. Keysser's further experience (1914) was also discouraging. C. Lewin, 1928, interpreted the effects of colloidal metals and of arsenic as nonspecific actions on the capillaries of the tumor. Carcinomatous tissue of mice shows some selective concentration of bismuth, after hypodermic injection, but not of lead or thorium (Hevesy and Wagner, 1930). The injection of lead will be discussed under that heading. *In tissue cultures* of a rat sarcoma, the addition of zinc or copper hindered growth. Minimal quantities of iron increased the growth rate and emigration of the cells; moderate concentrations increased the oxydase granules; higher concentrations retarded growth and finally caused degeneration (Uei, 1926). The biochemistry of malignant tissues was *reviewed* by Voegtlin, 1937. In human cancer, the reported improvement has been symptomatic only, and this has little significance. Weil, 1913 and 1915, pointed out that the only admissible sign of improvement is reduction of the size of the tumor; from this standpoint the clinical reports are negative.

INORGANIC ARSENIC COMPOUNDS

Arsenical compounds act locally as mild and slow corrosives and have been employed in superficial cancer. Systemically, they relax the capillaries and increase their permeability, thus simulating inflammation. This change is most conspicuous in the splanchnic area. In acute arsenic poisoning, it results in violent gastro-enteritis, closely resembling cholera. The dilatation of capillaries introduces changes in the circulation which cause secondary disturbances in the function of more remote organs, particularly in the *nervous system;* but the latter are probably direct, for they occur acutely in frogs whose nervous functions are not immediately influenced by the blood supply. *Fatty degeneration* of the cells is seen, especially in glands and muscles, with other disturbances of nutrition and metabolism, particularly in chronic poisoning. There may also be a direct paralysis of the *heart.* Milder degrees of the same action may stimulate metabolism beneficially. This might explain the therapeutic uses of arsenic in malnutrition, anemias and skin diseases; but the mechanism of their action, and indeed the results, are in doubt. There are also characteristic effects on the bones and bone marrow. Arsenic, especially in the organic forms, is highly effective against protozoan infections.

Arsenous and Arsenic Compounds.—Trivalent As (arsenites) is generally much more toxic for protozoa, bacteria and yeast cells than is pentavalent As (arsenates) (Kionka, 1911). This holds also for the different valence in organic compounds, and for the corresponding antimony valences (Friedberger and Joachimoglu, 1917). It has been assumed that the 5-valent As is nontoxic until it has been reduced to the 3-valent (Loew, 1887).

The following shows the relation of the inorganic trivalent and pentavalent compounds:

As^{III}: AsH_3 = arseniureted hydrogen
As_2O_3 = arsenous trioxide
$+H_2O = H_2As_2O_4 = 2HAsO_2$ = arsenous acid
$KAsO_2$ = potassium arsenite
$KH(AsO_2)_2$ = potassium acid arsenite

As^{V}: As_2O_5 = arsenic pentoxide
$+H_2O = H_2As_2O_6 = 2HAsO_3$ = arsenic acid, meta
$+3H_2O = H_6As_2O_8 = 2H_3AsO_4$ = arsenic acid, ortho
Na_3AsO_4 = sodium arsenate
Na_2HAsO_4 = sodium arsenate, dibasic

Relative Toxicity of Arsenic Compounds.—With intraperitoneal injection into guinea pigs, the toxicity decreases in the order of: arsenites, arsenates, colloidal arsenic, atoxyl and cacodyl (Launoy, 1918). *Elementary arsenic* (precipitated) has one-fortieth the toxicity of the trioxide, hypodermically, for rabbits and guinea pigs (Cannava, 1938). The *ratio of toxicity of arsenous acid: arsenic acid* varies for different tissues. With intravenous injection in rabbits, it is as 6:10; for the excised frog's heart, as 300:1. The arsenous is also more toxic for the excised intestine of rabbits. These different ratios indicate that the toxicity of arsenic acid is due to reduction to arsenous acid, which varies in degree for different tissues (Joachimoglu, 1915). Schulz, 1884, and Binz, 1897, attempted to explain the arsenic effects as *alternating oxidation and reduction* of the cells, due to the easy passage of arsenous and arsenic compounds into each other (which Schulz, 1892, demonstrated on organ emulsions). Husemann, 1892, pointed out that if this were true, both forms should have the same toxicity. The difference is not great for mammals, but considerable for lower animals and plants (O. Loew). The explanation is therefore not tenable. It is now generally believed that the arsenicals hinder protoplasmic oxidation. Relatively low concentrations of arsenic arrest assimilation of oxygen by rabbits' liver, yeast, bird erythrocytes, and insects. Arsenous oxide inhibits various oxidation systems (P. P. Cohen, 1939). Peters *et al.* found that sodium arsenite and lewisite check the pyruvate oxidase system of brain mash, which depends on the —SH group for its activity. It appears that trivalent arsenicals are toxic by combining with the —SH group of the activating proteins of enzyme systems, which are concerned in carbohydrate transformation and fat metabolism. Voegtlin, Dyer and Leonard, 1923, showed that the arsenous oxide binds and thus inactivates organic *sulfhydryl groups,* especially glutathione, and conversely, glutathione antagonizes the toxic and therapeutic actions of arsenicals (S. M. Rosenthal and Voegtlin, 1930).

Absorption of inorganic arsenicals occurs readily, to some extent even from the intact skin. Poisoning may therefore result from the external use of arsenical cosmetic preparations. With hypodermic injections, the diarrhea often sets in within an hour.

Excretion occurs by all the usual channels—urine, feces, sweat (Tachau, 1911), milk and epithelium of the skin (Heffter, 1905). With oral administration, the main part leaves by the feces; with hypodermic, almost completely by the urine. The excretion is always slow and incomplete, especially with prolonged administration (Croner and Seligmann, 1907).

Time of Excretion.—The excretion begins in two to eight hours after the administration, but lasts for a long time—three to ten days, after a single dose; to seventy days when it had been given continuously. In rabbits' urine it was found for 120 days, in dogs' for 160 days, after the administration was stopped. The elimination and retention in dogs were studied by Dutcher and Steel, 1914.

Retention.—A considerable proportion of arsenic is retained even at low income levels, increasing greatly with higher income. It is stored in all the tissues.

The storage of arsenic with long-continued feeding of subtoxic doses to rats and dogs has been studied extensively by Calvery and his associates, 1938. The storage was much greater when arsenic was fed as calcium arsenate than as the trioxide (H. J. Morris, 1938). Dogs store much less than rats at the same intake level; and both store much less than they do of lead.

Distribution in the Tissues.—The *kidneys and liver* have by far the highest arsenic content of the viscera, and the concentration in the kidneys is much the higher. That in the *cerebrospinal fluid* is low. The hair has a high concentration in chronic poisoning. The arsenic passes across the placental circulation of the *fetus* (Laug *et al.*, 1938).

Radioactive potassium arsenite injected hypodermically into man, apes, rabbits, and guinea pigs shows the highest concentration in the kidney and liver, lower concentration in the blood. In leukemic blood there is ten times as much arsenic per leukocyte than per erythrocyte. Rats have the highest concentration in the blood; 95 per cent of the blood arsenic is in the erythrocytes, and follows the globin and heme fractions (F. T. Hunter *et al.*, 1942). Extensive and accurate data for continued feeding of rats and dogs are given by H. J. Morris, 1938, and E. W. Wallace, 1938. Morris noted that the *weight of the liver* averages 41 per cent heavier than in the control animals, while that of the brain was 8 per cent less. Slowtzoff, 1922, claims that the arsenic exists in the liver as a nucleoprotein compound. Older data for animals are reported by Blarez and Deniges, 1907; for *human* by Eckeley, 1913, and Schellbach, 1922; *cerebrospinal fluid* by Eckeley and by Finel and Leroid, 1913. After the administration of arsenic, the *hair* contains detectable quantities, in firm combination. The deposition is slow but persistent. Therefore none is found in acutely fatal poisoning, the earliest demonstration being after two weeks. It may then persist for months or years, long after the metal has disappeared from the liver and bones or from the skin (Heffter, 1915; M. Oppenheim and Fantl, 1934).

Normal Occurrence of Arsenic.—A Gautier, 1899, found minute traces of arsenic in normal tissues. Its universal presence was confirmed by Bertrand and all those who worked with sufficiently delicate methods (C. N. Myers and Cornwall, 1925). In man, it occurs especially in the thyroid (0.16 mg.); also in the thymus, brain and skin. It appears to be in organic combination with the nuclein. None is found in the liver. Normal human blood contains 0.064 mg. per 100 cc. (H. Guthmann and Grass, 1933). This arsenic is introduced with the food and especially the drinking water. The quantity of arsenic normally present in the intestinal canal *never* exceeds $\frac{1}{10}$ mg. Larger quantities point to poisoning (Gautier, 1904). The *urine* generally contains traces, up to 0.5 mg. per day, depending mainly on the arsenic content of the food (I. Bang, 1916).

Local Actions.—The arsenicals are not precipitant and therefore irritate only weakly, even on wounds or mucous membranes; but the cells die slowly after prolonged contact. This is due to injury of the capillaries, which results in congestion, stasis, thrombosis, leading to local ischemia and necrosis. There is no direct action on the cells, for the cornea, which does not have capillaries, is not injured, nor are dead tissues corroded (J. Witzel, 1898; Ellinger, 1931). The destructive action is sometimes used for killing exposed *dental nerves* and superficial *epitheliomas*. Arsenic is much more destructive to pathologic cells, so that the cancerous tissue may be killed without injury to the surrounding normal tissue. As with all cancer salves, some of the deeper tumor cells generally escape, leading to inoperable recurrences. Their use is therefore inadvisable. Relatively benign epitheliomas may be caused by prolonged arsenic contact (H. Montgomery and Waisman, 1941).

Circulation.—Fall of blood pressure to shock level is characteristic of acute and subacute arsenic poisoning. It is due to paralysis and increased permeability of the capillaries, analogous to traumatic shock, enteritis, and peptone or histamine injection. The vasodilatation is most conspicuous in the splanchnic area; but the blood pressure falls even when the intestines are tied off, so that the muscular vessels are also dilated. The dilatation can be demonstrated by perfusion of excised organs. It is therefore peripheral. The vessels, however, continue to react to splanchnic stimulation till very late, and to epinephrine even after the splanchnic response is lost (A. Loeb, 1911). The arterioles must therefore still be capable of contracting.

Intravenous injections of large quantities of salt solution cause edema in animals poisoned with As, but not in the normal (Magnus, 1899). The thoracic *lymph flow* is increased by arsenic, the phenomena being similar to those of peptone (Yanagawa, 1916). The application of arsenite to the exposed *mesenteric vessels* of the frog or rat causes dilatation, first with faster flow. Soon the capillary walls become altered and the flow is slowed, with diapedesis of corpuscles (Ellinger and Schmidt, 1933). However, arsenic inhibits the migration of leukocytes in the inflamed mesentery of frogs (Ikeda, 1916). Since *increased permeability* of the capillaries is one of the essential features of inflammation, the phenomena of arsenic poisonings are similar to those produced by irritating inflammation, although the primal cause is different.

Heart.—In the excised (Langendorff) heart the amplitude is first increased, then diminished; the rate may be slowed, quickened or arrhythmic. Arsenites are more toxic than arsenates, and these more than the organic.

Of the latter, cacodylate is the most potent; arsphenamine and its oxidation products are inactive (Archangelski, 1912). In intact animals the cardiac action of the arsenicals is relatively unimportant, for the heart is able to maintain a fairly high pressure if the aorta is clamped (Boehm and Unterberger, 1874).

Gastro-Enteritis.—The first and principal symptoms of acute arsenic poisoning are those of violent inflammation of the digestive tract. This suggested that arsenic acts as a corrosive. However, the autopsy rarely shows extensive corrosion, and the gastro-enteritis may be obtained with at least equal readiness if the arsenic is injected into the circulation or subcutaneously. This would not definitely exclude all local action, since some arsenic is excreted into the alimentary canal, but the quantity is not nearly enough to account for the symptoms.

The inflammation is due to the systemic action on the capillaries, which is strongest in the intestines, no matter how the arsenic has been introduced. The capillary paralysis results in the production of exudation into the connective tissue. This raises the epithelium and causes it to be thrown off in shreds or false membranes. The exudation is then poured into the lumen of the intestine and largely coagulates. This distention, as well as the circulatory changes, causes increased peristalsis and *watery diarrhea;* the shreds of mucus and coagulated exudation give to the evacuation the character of "*rice water*" stools (Boehm and Pistorius, 1882). The pathology is the same as that of Asiatic cholera, and without a history it is impossible to distinguish between the two conditions except by chemical examination of the dejections. The extreme distention of the capillaries may lead to their rupture, to the formation of ecchymoses, or possibly bleeding into the intestine or stomach, and consequently bloody vomiting or diarrhea.

Kidneys.—Arsenic produces nephritis, at first mainly vascular (Schlayer and Hedinger, 1907), but always with more or less involvement of the epithelium (MacNider, 1912).

The vessels of the kidneys participate in the capillary dilatation. The glomerular capillaries are swollen so as to fill the capsule; the urine is albuminous and scanty, and cannot be increased by caffeine (Hellin and Spiro, 1897). The retention of nitrogen in the blood is relatively slight (Karsner and Denis, 1914). The types of nephritis from different arsenic compounds, and the actions of arsenicals on the *adrenals* are described by L. Pearce and Brown, 1915.

Muscle Metabolism.—Acute arsenic poisoning of rabbits decreases the concentration of hexose monophosphate and adenyl pyrophosphate in the muscle (Nonnenbruch *et al.*, 1936).

Etiology of Arsenic Poisoning.—Arsenic trioxide, "white arsenic," was formerly used extensively for *criminal poisoning.* It is readily obtainable, and is easily administered without suspicion, since it is odorless and nearly tasteless. The symptoms also are not likely to arouse suspicion, the acute and subacute course resembling that of a severe gastro-intestinal upset, which by repeated graduated administration may take the color of indefinite ailing, with nephritis, neuritis, and so forth. An Italian woman, Tofana, at the end of the 17th century was credited with special skill in such poisoning by an "*Aqua Tofana*" prepared from the putrefied juices of animals poisoned with arsenic. However, much of the traditional poison lore of former centuries smacks of the witches' cauldron. The development of chemical methods of detection has changed this situation. Among the ignorant, however, it may still be unsuspected. The use of arsenical embalming fluids constitutes a difficulty in its medico-legal detection, which is also complicated if arsenical medicines have been administered. *Accidental or suicidal* acute arsenic poisoning is still common, since arsenic is easily accessible as arsenic trioxide in rat and fly poisons, and as insecticides, lead or calcium arsenate, and Paris green. Arsenic trioxide when sold at retail should be colored with lamp black or indigo so that it may not have the innocent appearance of powdered sugar. *Therapeutic arsenic poisoning* may occur subacutely by special susceptibility to the organic arsenicals; inorganic arsenic therapy may easily lead to chronic poisoning. *Chronic arsenic poisoning* arises chiefly from arsenical cosmetics, dyes and fabrics, and from foods contaminated with insecticide sprays. Many of the cosmetic preparations on the market contain arsenic and have given rise to accidents. The use of arsenic compounds, such as Schweinfurt green, as pigments has been absolutely prohibited; but many of the coal-tar dyes require arsenic in their preparation, and frequently this is not entirely removed.

Arsenical Dyes.—Wall paper dyed with arsenic compounds was formerly a frequent source of arsenic poisoning, but this has now largely disappeared. The arsenic is given off from these papers as dust. Undoubted cases of poisoning have also occurred, however, when the arsenical paper was completely covered by a harmless paper; in these, some volatile arsenic compound must have been formed. Modern wall papers contain practically insignificant traces (Schulz, 1915). The permissible limit of arsenic in papers is placed at 0.1 grain per square yard; but this is probably not quite harmless. The Bureau of Chemistry of the United States Department of Agriculture has analyzed a number of papers on the American market (Haywood and Warner, 1904). Over 90 per cent of these contained less than 0.046 grain per square yard, and are therefore safe. *Furs, rugs and fabrics* were less satisfactory. *Black stockings* particularly often contained quantities of arsenic (above 0.01 grain per square yard), which must be deemed dangerous, considering their intimate contact with the skin.

Arsenic in Foods.—The use of arsenical insecticides has become practically indispensable in agriculture, but they entail some danger to health unless they are carefully controlled. Arsenic is used chiefly as Paris green, and as calcium arsenate and lead arsenate, the last involving also the more serious risk of lead poisoning (H. A. Kuhn, 1930). Fruits and vegetables subjected to these sprays contain the metals for long periods (Sonntag, 1915), particularly in the exposed outer layer. They can, however, be removed by suitable washes to insignificant and harmless proportions.

The United States food control regulations limit the quantity of spray residue permitted in food. The current limit for arsenic is 0.01 grain per pound, 1.4 mg. per Kg. If three pounds of food consumed in a day contained this concentration, it would amount to 0.03 grain = 1.95 mg. of arsenic. The allowance for lead is nearly twice as high. The use of arsenates in sprays between 1917 and 1936 in the United States increased from 14.5 to 125 million pounds per year, a pound per person (Calvery, 1938).

When fed to rats over long periods, calcium arsenate is more toxic than lead arsenate, and this is more toxic than lead carbonate (L. T. Fairhall and Miller, 1941). Orchardists exposed to the lead arsenate spray routine have a urinary arsenic concentration of 0.06 to 0.22 mg. per liter; nonexposed individuals have 0.03 to 0.15 mg. The difference is not considered practically significant (P. A. Neal *et al.*, 1941).

Arsenical insecticides are the most extensively used "*stomach poisons*" that kill insects after they are eaten. They produce desquamation of their intestinal epithelium (M. Pilat, 1935). Arsenates (lead or calcium) are more useful, since arsenites are relatively more injurious to *plants*. Somewhat high concentrations kill the leaves outright, blackening them in a day or two. Smaller amounts have no perceptible effect for some weeks; then the leaves turn yellow and drop. Still smaller amounts increase the respiration of the foliage. Arsenic-sprayed citrus trees mature their fruit faster. *Lead arsenate*, the most used arsenical insecticide, is relatively insoluble, but is partly hydrolyzed by water to basic lead acetate and arsenous acid (McDonnell and Graham, 1917) and may therefore scorch the foliage. *Paris green*, aceto-arsenite of copper, has also been used for *malaria control* by dusting it on the pools, where the particles are eaten by the larvae. *Arsenic trioxide* and *sodium arsenite* are used on insect baits, never on the foilage. Sodium arsenite is also employed to kill *weeds* (H. H. Shepard, 1939).

Course of Acute Arsenic Poisoning.—The symptoms appear only after several hours, and sometimes on the next day; illness occurring promptly after eating the suspicious food is probably not arsenical. Once started, the course may be rapid: in *fulminant cases*, the withdrawal of the blood from the general circulation into the splanchnic area may produce prompt collapse, convulsions, paralysis, unconsciousness and death before enteritis has time to develop (corresponding to "dry cholera"). The typical course, however, extends through eighteen hours to three days and sometimes four to fourteen days. The suspicion of the patient may have been aroused by the sweetish astringent taste of the substance. The *symptoms* start with vomiting and profuse and painful diarrhea. The withdrawal of water from the body leads to great thirst, dryness of the mouth and throat, and difficulty in swallowing and articulation. The urine is diminished and often bloody and albuminous. The nervous symptoms consist in vertigo, headache and pain in the limbs. The patient is cyanotic, with cold extremities. Toward the end occur syncope, coma, clonic and tonic spasms and general paralysis. A deceptive remission may occur on the third or fourth day, with cessation of the vomiting and diarrhea and with apparent improvement in the general condition, but with recurrence of the collapse within a day. Death usually occurs by exhaustion as a result of the prolonged gastro-enteritis, as in cholera. In case of recovery, the symptoms gradually regress, but severe diarrhea may persist for weeks and sometimes finally weaken the patient to a fatal termination. In the *subacute poisoning* the inflammation of the mucous membrane of the alimentary canal is prominent. Inflammation of other mucous membranes also becomes conspicuous, and shows as conjunctivitis, coryza, stomatitis, salivation and pharyngitis. Skin eruptions make their appearance if the arsenic poisoning is at all prolonged. In this case there are also symptoms arising from the central nervous system, as well as neuritis. The *diagnosis of acute arsenic poisoning* is made by the violent gastro-enteritis. This can usually be easily distinguished from that produced by acids and alkalis, by the history of the case, absence of corrosion in the mouth, and by the lesser prominence of the local symptoms.

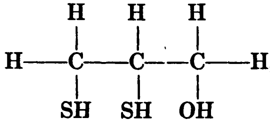
Autopsy Findings.—The patient appears emaciated from the withdrawal of liquid from the body by the profuse diarrhea, and this even if he retains a fair amount of adipose tissue. The appearance of the alimentary canal with its large amount of fluid and the presence of shreds of mucus and false membrane, with usually no pronounced corrosion, are characteristic. Microscopically, gastro-adenitis and cell infiltration are often seen. The body after arsenic poisoning usually putrefies slowly and may become mummified, which causes a suspicion, although it is not at all a proof of such poisoning. The positive proof is furnished only by the chemic examination. It must not be forgotten that arsenic may be introduced into the body in the embalming fluid.

Treatment of Acute Poisoning.—Acute arsenic poisoning is best treated by emetics and gastric lavage with warm water followed by a saline cathartic. The kidneys would be protected by a milk diet. The chemic antidotes are of doubtful value. *Magma Ferri Hydroxidi* (see Index) was introduced by Bunsen and Berthold, 1834, and was long considered the best antidote, the ferric hydrate and arsenic forming a compound which was deemed almost insoluble; but experienced pharmacologists (De Busscher, 1902; McGuigan *et al.*, 1923) found that the antidote at best postpones death for a few hours, and apparently gives a slightly smaller percentage of fatalities; the differences may lie within the experimental error. It is conceivable that this antidote and other colloids may somewhat delay absorption by absorbing the arsenic (Lockemann and Paucke, 1911), and its administration can do no harm, provided that it is *promptly followed by effective evacuation.*

Para-aminobenzoic acid administered to rats diminishes the renal lesions and the mortality ratio of pentavalent arsenic and antimony compounds (P. N. Harris, 1944).

The hypodermic injection of *magnesium sulfate* has saved animals from fatal doses of arsenic, even when the latter was also injected hypodermically. Presumably, difficultly soluble arsenic magnesium compounds are formed (Sieber, 1912). The antidote must be used promptly, and the effective dose of magnesium is itself dangerous.

Dimercaptopropanol, "*BAL*" ("*British Anti Lewisite*"), Dimercaprol, 2,3-dithio-propanol, "dithiol,"



$$\begin{array}{ccccccc} & & H & & H & & H & \\ & & | & & | & & | & \\ H & — & C & — & C & — & C & — H, \\ & & | & & | & & | & \\ & & SH & & SH & & OH & \end{array}$$

was developed during the war especially as an antidote to the arsenical lewisite "gas," and is effective against other arsenicals, mercury, gold, antimony, bismuth, cobalt and nickel. It is ineffective against lead and selenium, and additive with tellurium (H. A. Braun *et al.*, 1946). Excessive doses are directly toxic. It is recommended against untoward effects of intensive arsenic therapy. Mercury poisoning appears to require larger doses (reviews, L. L. Waters, 1945; A. Gilman, 1946; Council on Chemistry and Pharmacy, report, 1946, J.A.M.A., *131*:824. A symposium of papers appeared in the J.P.E.T., 1946, *87*, No. 4, Suppl.).

Mechanism.—Dimercaptopropanol and closely related dithiols have a greater arsenic affinity than do the tissue thiols, and so prevent and remove the inhibition of enzymes by lewisite and other arsenicals. However, dimercaprol is directly toxic to some enzyme systems. It is a potent reducing agent and is rapidly oxidized by catalytic amounts of copper and hemin. It instantly reduces methemoglobin to hemoglobin and destroys this and hemin by opening the porphyrin ring. The *cytochrome oxidase activity* is arrested by preventing the oxidation of cytochrome. Brain glycolysis is inhibited by combination with the metal protein components that take part in the enzymatic process. Oxidized dimercaptopropanol inhibits enzyme systems containing essential -SH groups It destroys the activity of *insulin*, possibly by reducing its -S-S- groups. The inhibitory effects of *other heavy metals* on succinoxidase are removed by certain dimercaprol derivatives, indicating that the toxicity of these metals also is due to inhibition of -SH enzymes.

Dimercaptopropanol mobilizes the tissue arsenic in cats treated with oxophenarsine, producing a sharp rise in the arsenic concentration of the plasma (W. F. Riker and Rosenfeld, 1946).

Systemic symptoms after administering dimercaprol to man, 3 to 5 mg. per Kg. intramuscularly, consist in paresthesias (tingling of the nose, eyes, mouth and skin); perspiration and feeling of warmth, pain in various regions, lacrimation, blepharospasm, salivation, vomiting; restlessness, apprehension, weakness, fatigue, quickened heart rate, usually rise of blood pressure. These symptoms generally subside in one-half to four hours. With 8 mg. the effects are more marked, but return to normal in an hour or two. Repeated administrations, 5 mg. every three hours, do not produce significant cumulation, but rather some tolerance in some cases (H. Gold and Cattell, 1946). The same symptoms are shown by dogs. *Larger doses* produce increased depth and rate of respiration; muscle tremors of gradually increasing intensity; rapid thready pulse, nystagmus; *finally,* repeated tonic and clonic convulsions, acidosis, coma and death. The convulsions are alleviated by anesthetics and barbiturates (J. H. Durlacher *et al.,* 1946). Intramuscular or percutaneous administration causes intense vasoconstriction in skin and muscles, resulting in transient rise of blood pressure. Rapid intravenous injection produces circulatory collapse and direct cardiac injury (M. B. Chenoweth, 1946). *Pathologic* changes are slight: some congestion of the viscera, and sometimes fluid in the serous cavities and lungs. The LD_{50} for rats is 105 mg. per Kg. The actions on isolated skeletal muscle of frogs are reported by S. Krop, 1946.

Local application to the skin produces erythema and edema, but not vesication or necrosis. It is intensely irritating to the respiratory and gastric *mucous membranes,* causing edema and ulceration. In the eye, 10 per cent solution in oil produces temporary lacrimation, blepharospasm and pain, but no lasting ill effects.

Percutaneous application produces the typical systemic effects on the circulation (Chenoweth, 1946).

The pharmacology of several substances related to dimercaprol is described by Chenoweth *et al.,* 1946, and by O. G. Fitzhugh, Woodard *et al.,* 1946.

Effectiveness against Arsenical Poisoning.—Dimercaptopropanol seems effective in arsenic poisoning in man. It protects completely against *local effects of lewisite* on the skin, even when erythema has started. In the eyes it furnishes marked protection up to five minutes, and improvement up to thirty minutes. It protects contaminated animals against the *systemic effects of lewisite* or phenyldichlorarsine also when it is applied at a distance, and increases the excretion of arsenic. It should be applied to the burned area and administered systemically (H. E. Harrison *et al.,* 1946). It is effective against acute and subacute *oxophenarsine poisoning* in rabbits and cats, the arsenic being removed from its combination in the cells and excreted as the relatively nontoxic thioarsenite (H. Eagle, Magnuson and Fleischman, 1946; W. F. Riker, 1946). It resuscitates *micro-organisms* poisoned by various trivalent arsenicals, including oxophenarsine.

It is effective against clinical arsenic poisoning, as well as in animals, decreasing the mortality and hastening recovery (H. Eagle, 1946). Its value in arsenical dermatitis is reviewed by M. B. Sulzberger and Baer, 1947

Dimercaptopropanol decreases the toxicity of some *antimonial drugs,* notably tartar emetic and stibanose, but increases the mortality with fuadin, neostam and neostiban (J. F. Gammel *et al.,* 1947). It gives some protection in acute *mercuric chloride poisoning* (recovery of twenty-two patients: W. T. Longcope and Leutcher, 1946), and appears successful in serious poisoning by *gold* (A. Cohen *et al.,* 1947), even with the granulocytopenia (L. M. Lockie *et al.,* 1947). It also prevents the pulmonary reaction to inhalation of *zinc and cadmium fumes.* With cadmium, however, it forms toxic complexes in the body which cause serious renal damage. It is probably effective against *arsenical dermatitis and encephalitis,* but probably not against the hepatitis.

Dosage.—Dimercaptopropanol (BAL) is unstable in watery solution. It is marketed as a 10 per cent solution in oil, with 20 per cent of benzyl benzoate, which is administered intramuscularly. The dose schedule against *arsenic* is 3 mg. per Kg. of body weight, every four hours for the first two days, then four injections on the third day and two injections daily for a further ten days or until recovery. Against *mercury,* the first dose should be 5 mg. per Kg., as early as possible, followed by 2.5 mg. per Kg. in one or two hours, and again in two and in four hours; two such injections are given on the second day, and one on the third.

The mortality in acute clinical arsenic poisoning is high, 50 to 75 per cent (Lewin). The *fatal dose* varies, especially with the solubility of the preparation. Of the trioxide, 5 to 50 mg. are toxic; 0.1 to 0.3 Gm. is usually fatal; but recovery may occur after much larger quantities.

The dry trioxide or ordinary white arsenic is so slowly soluble that its toxicity is greatly influenced by the *fineness of the powder* in which it is taken; for instance, it requires 500 times more of the coarse powder than of the solution to produce emesis (Schwartze, 1922). The U.S.P. therefore specifies the maximal size of the particles in powders that are to be administered in solid form. *Pure metallic arsenic* is not very poisonous, nor are the pure *sulfides,* but they are generally contaminated with toxic oxides.

Parenterally, arsenic in solution is as toxic when injected into the mesenteric, as by the jugular vein, showing that the liver neither neutralizes nor retains it. It is less toxic on hypodermic injection, since it enters into more slowly dissociated compounds with the tissue elements.

Resistance of Species.—Arsenic is toxic to all animals which have a central nervous system; also to most of the higher plants, but not to all lower organisms. Its antiseptic action is comparatively small. Newborn salamanders show marked tolerance. Among *mammals,* the resistance is greatest in mice; then come the hedgehog, rabbit, dog and cat (Willberg, 1913). The susceptibility of *rats* to arsenic trioxide is decreased by sexual maturity (E. Agduhr, 1941).

The toxicity is the same for splenectomized as for normal mice (Towels, 1916). The *penetration* of various arsenic compounds into living and dead cells was studied by M. M. Brooks, 1923, 1925.

Habituation and Tolerance.—The mountaineers of Styria and certain other regions consume arsenic once or twice weekly, as a general stimulant and tonic. There is evidence that they gradually accustom themselves to use with impunity quantities of arsenic trioxide (to 0.4 Gm. per day) which would produce serious toxic, irritant and cumulative effects in ordinary individuals (Tschudin, 1851; Knappe, 1875). This tolerance can also be induced in dogs and rabbits. Cloetta, 1906, attributed it to diminished absorption from the alimentary canal. However, tolerance may be induced by intraperitoneal injections in rats (E. R. Norris and Elliott, 1945). Hausmann, 1906, attributed it to increased excretion. The latter also showed that the corrosive action on the intestines is decreased by habituation. Withdrawal does not cause any abstinence symptoms, even if the arsenic has been consumed for years. Joachimoglu, 1916, finds that the absorption of small doses, in dogs, is not diminished by habituation.

Fibroblast cells in *tissue cultures* do not develop any tolerance to arsenic trioxide with thirty-eight passages through increasing concentrations (O. Bucher, 1942).

Tolerance to some organic arsenicals can be induced by repeated administration in rats and rabbits. With carbarsone and arsacetin it may attain to three times the fatal dose. It is more moderate for mapharsen, tryparsamide and most of the others; slight or absent for the arseno compounds, none for sodium arsenite or cacodylate. Tolerance induced by one organic arsenical confers more or less tolerance to other organic arsenicals, but not to inorganic; nor does treatment with the inorganic induce tolerance to the organic. Induced tolerance to tryparsamide does not decrease its efficiency against trypanosomes (Kuhs *et al.*, 1939).

Subacute and chronic arsenic poisoning may produce chronic gastro-intestinal catarrh, sometimes ulcerative; some kidney injury and degeneration, and considerable tendency to edema: swelling of the eyelids is an early indication of therapeutic overdosage. Other phenomena are likely to be more important, especially with organic arsenicals and in slow chronic poisoning. They affect particularly the skin, liver, peripheral nerves and bone marrow. Fatigue and loss of energy may be the only symptoms in light chronic poisoning. The *skin changes* are particularly characteristic. They may extend to the mucous membranes, especially the conjunctiva. They include disorders of the vasomotor innervation, with flushing, edema and hyperidrosis; eczema, acne, thickening and scaling of the epidermis, keratoses beginning on the flexor surface of the hands and feet and sometimes progressing to epithelioma (Franseen and Taylor, 1934); falling out of hair, detachment of the nails, herpes zoster and sometimes fatal exfoliative dermatitis. Some patients develop a peculiar and characteristic melanosis (melanodermia) beginning in parts normally more deeply pigmented. In contrast to Addison's disease, it does not involve the mucosae. It is not due to a deposition of arsenic, but to organic pigment granules in the epidermis and exterior layers of the cutis (Gans, 1914). *Polyneuritis* occurs, with various symptoms, atrophy of the muscles, disturbance and paralysis of sensation and of the special senses (blindness). The voice may be altered by paralysis of the vocal cords. Severe mental disorders are relatively rare. *Liver injury* involves especially fatty swelling which may compress the bile ducts, resulting in increase of the bilirubin content of the blood, and in visible icterus. Occasionally, acute hepatitis may be rapidly fatal, especially with the organic arsenicals. *Injury to the bone marrow* leads to exhaustion of the blood-forming mechanism, resulting in the picture of pernicious aplastic anemia with hyperchromia and leukopenia. The *diagnosis of chronic arsenic poisoning* may be difficult because the symptoms are sometimes obscure or resemble closely those of chronic lead poisoning. They differ in the electric reaction of muscle and the absence of the blue line on the gums, which are characteristic of lead. Chemical examination may be necessary for the definite diagnosis.

Actions on Bone Marrow and Blood Formation.—In normal animals, the effects of arsenic on the marrow are mainly destructive: atrophy of the fat cells, dilatation and multiplication of the capillaries; increase of the leukoblastic, but not of erythroblastic, cells (in contrast to hemorrhage). Larger doses cause hyaline degeneration and anemia. Similar changes are produced by other metals, organ extracts and peptones (Stockman and Charteris, 1903), by phenylhydrazine and by excessive irradiation of the bone marrow (Isaacs, 1928). Saneyoshi, 1913, found that ordinary doses of arsenic do not normally stimulate the production of corpuscles. It is conceivable, but not demonstrated, that it acts more positively in anemia; von Hoesslin, 1913, claimed restoration of hemoglobin and erythrocytes, decrease of lymphocytes and increase of neutrophils. The viscosity of the blood is sometimes slightly increased (Farmachidis, 1912). The *resistance of erythrocytes*, as judged by hypotonic hemolysis, is increased by therapeutic doses of arsenic in anemias. Hill, 1915, suggested this as an explanation of the clinical improvement. Arsenate increases the rate of glycolysis by human red corpuscles (H. K. Barrenscheen and Hübner, 1930).

The *effects on metabolism* resemble those of phosphorus: *therapeutic doses* check oxidation, and favor nutrition and growth, even in adults. The bones become larger and more compact. The condition of the skin is especially improved. The blood formation seems stimulated under suitable conditions. Gain of weight under arsenic is not always due to improved nutrition, for it may be simulated by edema.

Arsenic is probably not an important "trace element", for rats grow normally when practically deprived of it (E. Hove *et al.*, 1938). The *growth* of rats is markedly impaired by the continued administration of "therapeutic" doses of trioxide, *i. e.*, 0.015 to 0.05 mg. per Kg. per day, corresponding to $\frac{1}{60}$ to $\frac{1}{20}$ grain for man (Sollmann, 1921). *Excessive doses*, as with phosphorus, lead to increased excretion of nitrogen, loss of weight, lessened gas metabolism, fatty degeneration of tissues, acidosis, decreased functionation of organs, destruction of blood, icterus, inability of the liver to form glycogen. A further analogy with phosphorus poisoning is the *fatty degeneration of the liver cells*, more marked with inorganic than with organic arsenic compounds. With intravenous injection, this is localized around the central veins; with hypodermic, it is more general (Ullmann, 1914). Toxic doses produce degenerative changes also in the kidneys, capillaries and blood. Pathologic tissues—malignant lymphomata, syphilitic gummata, and so forth—are more susceptible and may be attacked even by therapeutic doses. Experimental tumors may also be liquefied and destroyed (Neuberg, Caspari and Loebe, 1912). Arsenic leads to *thickening of the bones* and filling up of the Haversian canals (Gies, 1877), which may possibly justify its use in *osteomalacia*, but practically it is unreliable. It diminishes the *storage of lead* in bones of rats by about half (L. T. Fairhall and Miller, 1941).

Inorganic Arsenic in Therapy.—This was formerly used extensively and indiscriminately, as an "alterative and tonic," in nutritional disturbances, neuralgia, rheumatism, arthritis, asthma, chorea, malaria, syphilis, tuberculosis, diabetes, skin diseases and every kind of blood disturbance. These uses have become more and more restricted, and replaced by better, more certain and less dangerous agents. Inorganic arsenic is capricious, unpredictable and uncontrollable both as to good and harm, but the harm is more certain and generally more frequent than the good; but it is still used in leukemias and anemias, in the latter as a supplement to iron; and in skin diseases.

Arsenic in Leukemia.—The results are not brilliant, but it usually improves the general conditions somewhat. The early, milder stages are most promising (Hahn, 1914).

Skin.—Arsenic is administered externally and internally to improve the nutrition of the skin and hair, and in nonparastic chronic skin diseases. It should never be used in acute inflammatory conditions. The results are often disappointing. Hartzell, 1908, considered it most successful in recent, slowly spreading psoriasis; in chronic stationary lichen; and of limited value in pemphigus. Its injudicious use is often harmful to the skin. Brown discoloration, especially of naturally pigmented areas of the skin, may appear long after the arsenic administration has been discontinued. Arsenic is used extensively in *veterinary practice*, to improve the appearance of horses by brightening the coat and increasing the subcutaneous (also the peritoneal) fat.

Glycosuria.—Arsenic treatment (not salvarsan) lessens alimentary glycosuria in dogs. It has no effect on epinephrine glycosuria (Begemann, 1912). It has been tried in *human diabetes*, but without much success. Arsenic poisoning causes rapid loss of glycogen from the liver, and leads to the formation of lactic acid. Small doses increase, larger doses retard, *autolysis* (of the liver; Lacqueur and Ettinger, 1912). Small doses increase the *catalytic action* of the blood; larger doses have little effect (Duncker and Jodlbauer, 1911).

Dosage.—The ordinary "tonic" dose of arsenic trioxide is 1 to 2 mg., $\frac{1}{40}$ to $\frac{1}{30}$ grain; of the liquid preparations, 2 to 3 drops, three times daily. For more energetic effects, it is aimed to establish a tolerance by beginning with small doses, and gradually increasing these until some local manifestation of the arsenic appears—usually diarrhea, colicky pains, conjunctivitis or swelling of the eyelids. As soon as these are seen, the amount must be diminished. The starting dose may be 3 drops of Solution of Arsenious Acid, or 5 mg. of the Arsenic Trioxide, three times daily, increased by 1 drop or 1 mg., every day. All the official liquid arsenic preparations contain the equivalent of 1 per cent of arsenic trioxide. They may be given in water; the trioxide in pills, often with iron. "Fowler's solution" is the traditional favorite, but as it is alkaline, it is subject to incompatibilities, *f. i.*, with alkaloids, which may be avoided by the Solution of Arsenious Acid, which has the same arsenic content.

Preparations.—**Arsenic Trioxide,** U.S.P. (Arsenous Anhydride, Arsenous Oxide, Arsenous Acid, White Arsenic); As_2O_3; occurs as a white powder, or irregular masses of two varieties; one, amorphous, transparent and colorless, like glass; the other, crystalline, opaque and white, resembling porcelain. Both are odorless. Slowly sol. in 30 (glassy) or 100 (powdered or porcelain) parts of water; in 15 of boiling water; sparingly in alc. Freely sol. in hydrochloric acid and alkalis. Dose, 1 to 3 mg., $\frac{1}{60}$ to $\frac{1}{20}$ grain. It may be prescribed as ***Solution of Arsenous Acid,** U.S.P. (Solution of Arsenic Chloride), arsenic trioxide dissolved in Dilute Hydrochloric Acid and therefore of acid reaction; or as *Solution of Potassium Arsenite*, U.S.P. (Fowler's Solution; Liquor Kali Arsenicosi), which is slightly alkaline, and therefore *incompatible* with alkaloidal salts (in addition to salts of iron and magnesium, lime water and tannins, with which all arsenic solutions are incompatible). The dose of either solution is 0.1 to 0.3 cc., 1½ to 5 minims. Both contain the equivalent of 1 per cent of As_2O_3.

ARSENIURETED HYDROGEN

This gas, AsH_3, also called *arsine*, has a characteristic garlic odor. It is toxic in dilution of 1:20,000; a few bubbles (0.3 to 0.6 Gm.) may be fatal to man. The susceptibility varies considerably in different species. The gas is produced in lead burning; by the action of impure sulfuric acid on metals; from ferrosilicon, and so forth. Its toxic action is due to its *affinity for hemoglobin*, with which it forms a compound in the corpuscles, where it is gradually oxidized to arsenic oxide. This destroys the corpuscles, resulting in extensive hemolysis and anemia (Stadelmann, 1882). The blood count falls in a few hours. The hemoglobin is excreted by the urine, beginning in the sixth to tenth hour. Within a week, 70 to 80 per cent of the corpuscles may become hemolyzed, the blood count falling to a million. Death occurs from loss of hemoglobin, producing anoxemia and often pulmonary edema.

The *clinical symptoms* of anoxemia develop usually several hours after exposure, and resemble those of mountain sickness. The milder cases exhibit weakness, malaise, vertigo, intense headache, followed by nausea, vomiting and epigastric pain. In severe cases, the vomiting becomes continuous and bloody and the liver and kidneys become painful. Jaundice, hemato- and hepatogenous, appears, with a peculiar bronze tint of the skin, from the blending of the yellow with the cyanotic pallor. The urine contains hemoglobin, methemoglobin, hematin and bile pigments. The kidneys may be blocked by the debris of the blood corpuscles, or anuria may result from asphyxia. Oliguria indicates an unfavorable prognosis. Nervous symptoms, neuralgias and neuritis, may occur as in other arsenical poisoning. The blood picture is that of severe secondary anemia. Death may result in two to six days, preceded by convulsions, delirium and coma. The mortality is about 30 per cent. Recovery may occur even with severe cases. It may be complicated by the phenomena of subacute arsenic poisoning, with delayed death from nephritis. The *treatment* includes repeated transfusion, inhalation of oxygen and abundant fluid intake.

In vitro, arsine hemolysis is prevented by several fat-soluble mono- and di-thiol compounds. Some of the dithiols, but none of the mono-thiols, protect the respiration of tissue slices. 2, 3-Dimercaptopropyl ethyl ether protects intact animals against the arsine (C. J. Kensler *et al.*, 1946).

Hydrides of *antimony, selenium, tellurium and germanium* produce similar hemolytic effects (S. H. Webster, 1946).

Fate of the Arsenic.—A large part of the arsenic absorbed as AsH_3 is found in the blood corpuscles, much more than in the plasma or in other organs, except the spleen, where it accumulates from the destroyed corpuscles. The next highest concentration is in the liver and kidneys. The excretion occurs chiefly by the kidneys (Thauer, 1934).

Chronic poisoning with AsH_3 has been studied on animals by Kiese, 1937. The effects are blood destruction, at first compensated by active regeneration of erythrocytes, which fails in time, so that a stationary level of anemia becomes established. The hemoglobin may fall by 60 per cent. Other organs show but little injury. The *arsenic content* of the organs was unequal, but highest in the spleen, liver, bone marrow, erythrocytes and hair. The corpuscles always contain more than the serum.

"Ferrosilicon" is a mixture of Fe and Si compounds, used in the manufacture of steel. In the presence of water or moist air (as in shipment) it liberates phosphoreted and arseniureted hydrogen, which have produced fatal poisoning (J.A.M.A., *55:* 781, 1910). The grades containing 30 to 70 per cent of silicon are much more subject to the decomposition, and are therefore more dangerous than those containing a greater or smaller percentage.

Garlic odor with arsenic is a characteristic feature under certain conditions. It is noted when the metal is burned in air to As_2O_3. Moulds growing on damp wall paper and other arsenicals produce it by forming *ethyl arsine*, $As(C_2H_5)_2H$. The odor is sometimes observed in arsenic vomitus (Gumprecht), and is probably due to reduction products. Garlic breath does not occur, or but rarely, in the therapeutic administration of inorganic arsenic compounds, but is strong after the use of cacodylates.

ORGANIC ARSENIC COMPOUNDS

Trivalent and pentavalent arsenic can be introduced into a large variety of organic molecules. In this nonionic condition it does not immediately produce the ordinary arsenic effects; but in the course of the oxidation and reduction and other cleavage which these organic molecules undergo in the body, more or less ionic arsenic is gradually split off, and this produces the ionic arsenic actions in a delayed and generally milder form. The decomposition is usually slow, and progresses through intermediate stages of simpler organic molecules, so that a considerable part of the arsenic is generally excreted in organic form, before the cleavage is completed. In the meantime, the original compounds and their organic derivatives have the opportunity to exert their distinctive effects. These are much less toxic to the higher animals than is ionic arsenic; they lack particularly the paralyzing action on capillaries. On the other hand, they are much more toxic to protozoan parasites, trypanosomes, spirochetes, amebae, plasmodia, and so on, so that their administration arrests these protozoan infections, especially syphilis, sleeping sickness and spirillosis. The compounds that are practically useful have relatively little parasiticidal action *in vitro*. Their full effect develops in the host as with most antiprotozoal agents, probably by checking the multiplication of the parasites. In the arsenicals it is partly due to transformation into more active cleavage products. The toxicity and efficiency of the organic compounds are determined by a number of complex factors, especially the relation of absorption, distribution, sojourn and storage, and the rate and course of the decomposition. In the digestive tract the organic molecules are likely to undergo toxic cleavage, so that they must generally be administered parenterally. The compounds of the arsphenamine type tend to form colloidal solutions, and their intravenous injection may produce colloidal reactions with the blood. These differ for the individual compounds and can be minimized by careful technic in the preparation and injection of the solutions.

Chemic Structure.—The therapeutic organic arsenic compounds may be arranged under those containing *pentavalent* arsenic (cacodylic acid, arsanilic acid, tryparsamide, carbarsone and the like) and those with *trivalent* arsenic, the arsphenamines and the phenarsines (mapharsen, and so on). The *arsenic content* of the compounds is of less importance than the manner in which it is combined.

Historical on Arsenic in Protozoan Infections.—Arsenic had some reputation in syphilis since Fallopius (Herzfeld, 1911), and the cacodylate was employed in this disease by Gautier in 1896. Arsenic was also used in malaria with fair success. Laveran and Mesnil, 1902, found that arsenous acid causes the temporary disappearance of trypanosomes from the blood of infected mice. It has been tried in human cases (Merck's Report, *21:* 223), but the really effective dose is too dangerous.

Chemotherapy.—This term was restricted by Ehrlich to the parasiticidal treatment of infections by chemical agents. Such "specific remedies" had been discovered empirically for several protozoan diseases: quinine against malaria; mercury against syphilis; and ipecac against amebic dysentery. Ehrlich, 1909, sought systematically to extend this field by the search for substances which would combine a relatively high toxicity for the parasites with a relatively low toxicity for the host; *i. e.*, which would have a favorable "chemotherapeutic index," a low ratio of

$$\frac{\text{(Minimal effective dose)}}{\text{(Minimal lethal dose)}}.$$

He assumed that the relative toxicity for parasite and host would depend chiefly on the selective affinity of these for the toxic agent, and believed therefore that the therapeutic index would depend on the ratio of "parasitotropism" to "organotropism" (Bechhold and Ehrlich, 1906). It is now recognized that destruction of the parasite *in vivo* often does not depend on the direct "parasitotropism" of the agent, but more generally on interferences with enzyme systems that are essential to the metabolism of the parasite. In analogy with sulfonamides, para-aminobenzoic acid is a highly effective antidote to otherwise fatal doses of organic pentavalent arsenic compounds for rats. So also are many other benzene derivatives, the isomeric para-aminobenzoic acids, benzoic acid, phenylacetic acid and others (J. H. Sandground, 1944). The tropism theory was only a working hypothesis, however, and was not directly involved in Ehrlich's work. This took the direction of determining experimentally the therapeutic index of a variety of substances, and culminated in the discovery of the trypanosomicidal dyes and arsenicals, and of the more widely applicable arsphenamine; and this in turn led to the introduction of the other parasiticidal metals.

The trypanosomes which cause the tropical "sleeping sickness" and similar diseases in animals are easily transmitted to white mice, and therefore presented a convenient test of therapeutic efficiency. Ehrlich and Shiga, 1904, studied in this way a great variety of substances. The search was at first haphazard; but when partly successful results were obtained, it was sought systematically to improve these by altering the side chains so as to increase their specific affinity for the chemoreceptors of the parasites. The effective trypanocidal agents found by Ehrlich and by independent workers belong to four groups: (1) Benzidine Dyes (Trypan Red, and so forth); (2) Basic Triphenylamine Dyes (Malachite Green, Parafuchsin, and so on); (3) Arsenic Compounds; and (4) Antimony and Bismuth Compounds.

Experimental investigations were important mainly by elucidating the general principles of chemotherapy, for it was soon found that the detailed results could not be transferred directly to man: Agents effective in one species of host were often much less effective in another. Nor can the results for one kind of parasite be transferred to another kind (Longley, Clausen and Tatum, 1939). The dyes in particular were not practical, since they cause intense coloration of the body, irritation and necrosis of the skin and severe cachexia. However, the trypanosome studies, with somewhat refined technic (Voegtlin and Smith, 1920; Dale and White, 1922), are useful for preliminary orientation. For antisyphilitic agents, the results should be checked on rabbits and mice inoculated with syphilitic virus (W. H. Brown and Pearce, 1916; L. Pearce and Brown 1922). The final clinical decision must rest with clinical tests on man. Ehrlich thought it essential that the parasites should be killed by one single massive dose of the antiseptic ("Therapia Magna Sterilisans"). Clinical experience has shown this to be generally impossible and fortunately also unnecessary. There may be advantage, however, in employing simultaneously or successively agents belonging to different groups; for strains resistant to atoxyl, for instance, need not be especially resistant to mercury (Nierenstein and Todd, 1907).

Acquired Resistance ("Fastness") of the Parasites.—Injection of ineffective doses of the chemotherapeutic agents may render the trypanosomes more resistant to the agents of the same group, although they preserve their susceptibility to the other groups (Ehrlich, 1907). The resistance is preserved for many generations, even if the resistant parasites are passed through a succession of hosts (Voegtlin, Dyer and Miller, 1924). The acquisition of drug resistance by spirochetes has not been demonstrated *in vivo;* it has been induced *in vitro, i. e.,* in cultures, but is lost in a few generations, so that it would not be important therapeutically (Akatsu and Noguchi, 1917). It is not known whether the fastness is a genuine habituation, or merely a selective survival of the more resistant strains; the latter appears more likely.

Splenectomy greatly decreases the effectiveness of arsphenamine against relapsing fever in mice (Kritschewski and Meersohn, 1926) and of tryparsamide and arsenoxide against trypanosome infections of rats, but in these splenectomy also increases the multiplication of the parasites in the untreated animals (H. M. Kelly, 1930); with scrotal implantation of syphilitic material in rabbits, splenectomy rather intensifies the spirochetocidal action of arsphenamine (W. Frei and Fröhlich, 1931). *Blocking of the reticulo-endothelial cells* with India ink decreases the curative effect of arsenicals on trypanosomiasis, although the serum of the blocked animals has a higher arsenic content and is more trypanocidal *in vitro.* The blockade has little effect on the storage of arsenic in the liver and spleen (L. Reiner *et al.,* 1932).

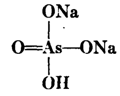
◆

SODIUM CACODYLATE

The effects of cacodylic acid (dimethylarsenic acid) are essentially those of the inorganic arsenic, to which it is partly reduced in the body. Since this reduction occurs but slowly, the action is more prolonged and less toxic, and the local irritant effects are avoided. However, the degree of reduction, and therefore of the effect, is variable. Cacodylate, especially when given by mouth, imparts a *garlic odor* [from cacodyl oxide, $As_2(CH_3)_4O$] to the breath, sweat, urine, and so forth. To avoid the more rapid reduction in the stomach, intestines and liver (Heffter, 1901), it is usually administered hypodermically or intramuscularly. Excessive doses produce *toxic symptoms,* due mainly to the ionic arsenic (Schulz, 1879; Heffter, 1901; Dawes and Jackson, 1907), although the cacodyl molecule may conceivably play a part. It is used *therapeutically* in the same condition as inorganic arsenic. The *dosage* is from 0.025 to 0.15 Gm.

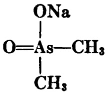
ORGANIC PENTAVALENT ARSENIC COMPOUNDS

These are illustrated by the following formulas:



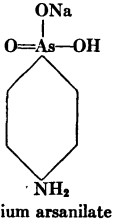
$$\begin{array}{c}\text{ONa}\\ |\\ \text{O=As—ONa}\\ |\\ \text{OH}\end{array}$$

Sodium arsenate

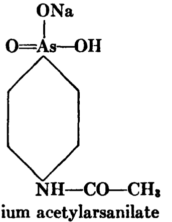


$$\begin{array}{c}\text{ONa}\\ |\\ \text{O=As—CH}_3\\ |\\ \text{CH}_3\end{array}$$

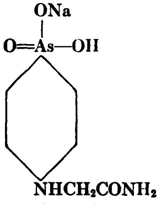
Sodium cacodylate



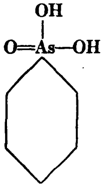
Sodium arsanilate (atoxyl)



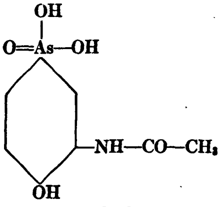
Sodium acetylarsanilate (arsacetin)



Sodium phenylglycinamide arsonate (tryparsamide)*



Paracarbamidophenylarsonic acid (carbarsone)



Acetylaminohydroxyphenylarsonic acid (acetarsone, stovarsol) per day, as pills; or hypodermically, as a freshly prepared warm sterile solution; also by enema.

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*The commerical product contains a half-molecule of water of crystallization.

Cacodylate is not effective in chemotherapy. The arsanilate derivatives are effective against trypanosomes, amebas, trichomonas and similar parasites, but are not very potent against spirochetes. They are quite toxic, and are likely to cause optic neuritis and blindness. Tryparsamide, which is less toxic, has a special field in neurosyphilis.

In *syphilis* it is ineffective even with doses that produced albuminuria and hematuria (intravenous injection of 0.5 Gm. every three days for 4 to 6 doses; Cole, 1916). Brayton, 1917, confirmed its lack of value, and pointed out that it produces fibrosis of the vein in nearly every patient and is sometimes followed by severe nephritis.

Fate of Cacodylate.—A part is excreted unchanged in the urine (on hypodermic injection, 6 to 10 per cent, Dawes and Jackson); but the greater part undergoes reduction, first to the volatile cacodylic acid, and a small part finally to inorganic arsenic.

A *bibliography* of cacodylate is given by de Biehler, 1907. It was introduced into therapeutics mainly by Gautier, 1899.

SODIUM ARSANILATE (ATOXYL)

This salt, sodium aminophenylarsenate, may be derived from sodium arsenate by replacing one hydroxyl by aniline. (It was at first believed to have a different constitution.) The name of "Atoxyl" is misleading, for the substance is quite dangerous. It had at one time considerable prominence as an organic form of arsenic, effective in all conditions in which arsenic is indicated; especially in sleeping sickness, in which it has been superseded by its less toxic derivatives; and in syphilis and other protozoan infections, in which it is greatly inferior to arsphenamine (Tomasczewski, 1908; Greven, 1910). The chief objection to "atoxyl" is the fairly frequent occurrence of *toxic effects*, especially permanent blindness, from therapeutic doses. These, as well as the therapeutic actions, are mainly due to the reduction products, probably trivalent, which are formed in the organism. Sodium arsanilate should not be given by mouth, since it is decomposed and rendered more toxic. The hypodermic dosage is from 0.02 to 0.2 Gm. every other day. The injections are said to be nonirritant.

This compound was first prepared by Bechamp in 1863, and its general actions were investigated by F. Blumenthal, 1902. It was then used as an arsenic substitute in skin diseases, anemias, and the like. Its toxicity to mammals is much less than that of arsenic trioxide, its acutely fatal dose being some forty times as great. H. W. Thomas, 1905, found it highly efficacious against experimental *trypanosome infections* of mice, and it was tried extensively in human sleeping sickness, especially by Robert Koch, 1907. It causes prompt disappearance of the trypanosomes from the blood, but they may recur, so that the injection must be repeated every seven days (R. Koch, 1907). Kopke's (1906) clinical results were less favorable. The parasites become gradually resistant. B. Moore *et al.*, 1907, recommended alternation with mercury, which acts on another stage of development (Hodges, 1908).

Toxic Effects of Atoxyl in Man.—Acute symptoms occur especially with doses exceeding 0.5 Gm. They resemble partly those of ordinary arsenic poisoning and consist in nausea and vomiting; colic, vertigo, general weakness and somnolence; neuritis, pain in limbs; deafness, retention of urine, sometimes nephritis; iritis and not uncommonly permanent optical atrophy (Hallopeau, 1907; Fordyce, 1911). Chronic poisoning presents the ordinary phenomena of chronic arsenic intoxication. The *eye symptoms* usually appear within a few weeks (in Koch's series only when the dosage exceeded 0.5 Gm.). They begin with scintillation, cloudiness, diminished vision and contraction of the visual field (Fordyce, 1911). The anatomic changes in animals as well as in man (Birch-Hirschfeld and Koster, 1910) show degeneration of the optic nerve and retinal ganglia, the retina being the more susceptible. The cerebral cells are also injured. *Inorganic arsenic and cacodyl* may also cause optic neuritis (of the nicotine type), but only rarely (Sulzer, 1911). Arsphenamine does not seem to cause the optic injury. Boyd, 1911, found in two human cases that arsanilate causes *nitrogen retention.*

Toxic Effects of Atoxyl on Animals.—The acute toxicity of atoxyl is perhaps one-fortieth of that of inorganic arsenic; injections have no acute effects on blood pressure. They produce, however, chronic effects and anatomic lesions, the distribution of which varies quantitatively in different animals (Igersheimer and Itami, 1909); dogs show mainly characteristic renal hemorrhages with secondary nephritis; cats exhibit mainly nervous symptoms with histologic lesions in the brain and cord. Rats and rabbits are intermediate. The *distribution of the arsenic* corresponds with the differences in effects. In cats, *f. i.*, the arsenic is found mainly in the nervous system; in dogs, in the parenchymatous organs (Igersheimer and Rothmann, 1911). Mammals also show the optic degeneration, both on local and systemic administration. (The toxicity of atoxyl was investigated experimentally by Cianni, 1908.) In *frogs*, Sanno, 1911, found that the toxicity is greatly increased by raising their temperature, presumably by favoring its transformation into more toxic products.

Reduction.—Since arsanilic acid is itself practically nontoxic to trypanosomes, it must undergo some changes in the tissues. The degree of decomposition and therefore the efficiency and toxicity vary in different animals. The decomposition products have not been isolated, but it is probable that they contain the arsenic in trivalent form. (Rothermundt and Dale, 1912, however, believed that it is directly trypanocidal.) The artificial reduction products, which vary according to conditions, are much more active than the arsanilate, and paraminophenol-arsenous acid kills the parasites in the test tube. B. T. Terry, 1912 found that emulsions of liver and blood reduce arsanilate into directly effective products.

Excretion.—After a single dose of arsanilate, the arsenic is excreted promptly and exclusively by the urine (Croner and Seligmann, 1907). With continued administration, the excretion is somewhat more prolonged; the greater part leaves within three days (Simonot, 1910), but traces continue to be excreted for three weeks (Welander, 1909). The effects are therefore somewhat cumulative. A small part leaves by the feces. Only a small proportion is excreted in inorganic form. A relatively large part of the arsanilate remains for a long time unchanged in the blood and tissues (Simonot, 1910), but a part is fixed and changed in the cells. The characteristic distribution in different animals is described by Igersheimer and Rothmann, 1909.

Sodium Arsanilate (Atoxyl) occurs as white, odorless crystals, of faintly salty taste. Readily sol. in water (1:5 or 6). Dose, 0.02 to 0.2 Gm. hypodermically every other day; gradually increasing if necessary until the single dose reaches 0.65 Gm. and until a total of 6.5 Gm. has been given. It must not be administered by mouth.

Arsacetin, sodium acetyl arsanilate, $C_6H_4(NH.CH_3.CO)AsO.OH.ONa.\ 4H_2O$, is less toxic acutely than arsanilate, and is highly parasiticidal in mice. In man, however, it is no more effective than the original substance, and is equally liable to cause blindness (J.A.M.A., 1910, *54:* 1559). It is even more likely to produce renal irritation (Borchers, 1910). Its only advantage is the greater stability, so that it can be sterilized without decomposition. The dosage, hypodermically, is 0.1 to 0.5 Gm. Ehrlich, 1907, noticed that some mice treated with arsacetin acquire a curious waltzing habit.

TRYPARSAMIDE

This pentavalent arsenic derivative, sodium phenylglycinamide arsonate, is highly effective in certain forms of trypanosomiasis (Tr. gambiense, African sleeping sickness and mal de caderas) and fairly successful in selected cases of cerebral syphilis. It also cures the "blackhead disease" of turkeys. Its parasiticidal action is more marked for trypanosomes than for spirochetes. It penetrates the tissues, including the central nervous sytem, more readily than most arsenicals. Its excretion is rapid, so that there is no cumulation. Its acute toxicity is low; doses corresponding to 4 Gm. of arsenic have sometimes been injected without bad effect; but even the smaller therapeutic doses usually produce more or less visual disturbance and sometimes permanent blindness. A few patients develop jaundice. Other untoward effects are unimportant and exceptional.

The compound was developed especially through the Rockefeller Institute; it was synthetized by Jacobs and Heidelberger, 1919; investigated on animals by W. H. Brown and Pearce, 1919; and in human trypanosomiasis by Pearce, 1921. Its application to neurosyphilis is due to Loevenhart and Lorenz of Wisconsin, 1922 and 1923.

Excretion.—About 70 per cent is eliminated in the urine within twenty-four hours; in part at least unchanged (A. G. Young, 1923).

Use in Trypanosomiasis.—In Trypanosoma gambiense infections, a single intravenous injection causes the complete disappearance of the parasites from the human blood; but they are likely to recur after three days to six months. If the injections are repeated in courses, the cure is complete and permanent (L. Pearce, 1921, 1939; Pearce and Brown, 1922). Other trypanosome infections (surra, dourine, nagana) are not so amenable. Tryparsamide is mildly toxic to trypanosomes *in vitro.*

Other Trypanocidal Drugs.—Tryparsamide and suramin are now used most extensively, but several aromatic diamidines appear promising, such as pentamidine, stilbamidine and propamidine (E. C. Faust, 1946). Especially good results are reported for *p-arseno phenyl butyric acid* in Tr. Gambiense before central nervous system involvement (H. Eagle, 1946).

Therapeutic Results in Neurosyphilis.—Tryparsamide probably does not act clinically as a treponemocide, for it is practically not effective against the primary and secondary stages of syphilis, nor against the gummata, and has apparently little effect in the early cerebrospinal manifestations. Its value is confined mainly to the disseminated sclerosis, before this has resulted in irreparable degeneration of the nerve cells. Loevenhart was inclined to attribute the effect to the provocation of local inflammatory reactions that would resolve the sclerotic lesions.

Of patients with early paresis, 40 to 50 per cent show improvement or complete remission. In tabes, the results are less striking, but there is generally some relief of pain and sometimes improvement of coordination. Most patients improve in physical condition and gain in weight. The Wassermann reaction decreases, but not parallel to the symptoms. Advanced cases of sclerosis are not benefited; they may, indeed, react with temporary exacerbation. The improvement in the early paresis is sufficiently frequent and marked to class tryparsamide as a valuable therapeutic agent, were it not for the risk of blindness. This must be carefully weighed. Tryparsamide generally would be restricted to cases of the type in which it has been most successful, and which have failed to respond to other treatment. It is used especially after malarial therapy, beginning with 1 Gm. and increasing gradually to 3 Gm. intravenously, with weekly intervals. It must be continued for months or years; less than a hundred injections give only transient improvement. Should the vision become blurred, the injections are intermitted for a time and resumed later.

Tryparsamide Amblyopia.—Minor temporary impairment of vision occurs in 10 to 50 per cent of the patients; both those with trypanosomes and with treponemas; in 5 to 10 per cent, the minor impairment remains permanent; in 1 to 5 per cent, the impairment is serious. The occurrence and outcome are at present largely unpredictable and unavoidable. However, they follow most frequently on the first injection, and do not seem to occur after the fourth injection; nor do they seem to occur in noninfected individuals. It would therefore appear that they are not due to the arsenical, but rather to an immunologic reaction. It is doubtful whether preexistent syphilitic optic lesion contraindicates or indicates tryparsamide.

The optic phenomena are discussed by A. C. Woods and Moore, 1924. The *pathological changes* in a case studied by Leinfelder, 1938, seven days after the onset of the blindness, consisted in acute degeneration of the retinal ganglion cells and of the innermost portion of the nuclear layer, with no evidence of primary degeneration of the optic nerves and tracts. There were no general pathological arsenic changes elsewhere. Treatment with increasing doses produced practically complete blindness in four out of five rhesus monkeys (Longley *et al.*, 1941). *Organic arsenic compounds produce blindness in monkeys* by decrease of retinal ganglion cells, proliferation of glial cells and demyelination of the optic nerve (B. J. Longley *et al.*, 1942).

Other Untoward Results.—The arsenical and direct toxicity of tryparsamide is remarkably low. Even minor disturbances are rare; the more common are dizziness and tinnitus; more exceptional are nausea, vomiting, nitritoid reactions, urticaria, mild dermatitis. A few patients are jaundiced. Skin eruptions may occur in patients with intolerance to trivalent arsenic (E. Epstein, 1939).

*Tryparsamide, U.S.P., sodium N-phenylglycinamide-p-arsonate, containing about 25.3 per cent of arsenic, is a white, odorless, crystalline powder; sol. in water (1:2). The solution is neutral to litmus. It should be freshly prepared each day and should not be heated or exposed to strong light or chemical fumes. Dose, *Caution!* intravenous, 2 Gm., dissolved in 10 cc. of sterile water. In trypanosomiasis this is administered twice weekly for twelve weeks. It should not be taken by mouth, but may be injected intramuscularly.

AMIDOPHENYLARSONIC ACIDS

Two derivatives, carbarsone and acetarsone, have been introduced chiefly as amebicidal agents. They are also potent against trichomonas and Vincent's angina. They are effective against syphilis, but much less so than the arsphenamines. They are administered by mouth. Their toxicity is relatively low. *Arsphenamines* have not been found satisfactory against amebiasis.

Carbarsone, paracarbamidophenylarsonic acid, was introduced as an amebicide by A. C. Reed, Anderson, David and Leake, 1932, as having the most favorable therapeutic index of the drugs which they tried. It is less toxic and more effective than acetarsone, but may produce similar untoward effects. It may be administered by mouth or rectum without interfering with the patient's ordinary routine. Its cost is relatively low. Its efficiency is high: in California, about nine-tenths of the patients respond satisfactorily to the oral administration, especially those with encysted amebae (the most frequent form in the United States), with or without acute or chronic symptoms, *i. e.*, including carriers. Those with motile amebae, usually with acute dysentery or diarrhea, are more resistant to oral treatment, and may require rectal injections (Anderson and Reed, 1934). There is no evidence of any prophylactic value. In rats with intestinal trichomonas, a single dose of 1 Gm. per Kg., by mouth or vein, proved permanently curative (Gabaldon, 1936).

Serious *untoward effects* are uncommon even with prolonged administration, up to fifteen months, but it is advisable to watch for cutaneous and other arsenical manifestations. Carbarsone should not be used in renal and hepatic disease, including amebic hepatitis.

Various dosages and velocities are being tried; indeed, the whole method is still on trial.

With 330 patients, only one, with acute hepatitis, showed serious intolerance. A few had slight gastric distress, in which impurities may have played a part. There was no evidence of damage of the kidneys, optic nerve, skin or other tissues (Anderson and Reed, 1934). Exfoliative dermatitis and other manifestations, usually mild, have been recorded by others (Report, Council on Pharmacy and Chemistry, J.A.M.A., *103:* 258), and one fatality with acute hepatitis, from a therapeutic dosage (Epstein, 1936). In animals, lethal doses produce lethargy, loss of weight, diarrhea and some degeneration of renal tubules (Reed, 1934).

Pemphigus is reported markedly improved by carbarsone, after three or four weeks, administering two capsules of 0.25 Gm. before breakfast for three days, then intermitting three days (R. P. Little, 1945).

Carbarsone, U.S.P. contains about 28.5 per cent of arsenic. It is a stable, white, almost odorless and tasteless powder, slightly soluble in water, freely soluble in dilute alkalis. It is usually administered *by mouth,* in gelatine capsules of 0.2 Gm., two or three times daily, to a total of 25 doses (*i. e.*, 5 Gm.). This course may be repeated several times if necessary, with rest intervals of ten days to prevent cumulative effects, since the excretion is slow. *Rectal administration* is substituted in resistant cases, or with acute symptoms: 2 Gm. dissolved in 200 cc. of 2 per cent sodium bicarbonate, on alternate nights, for a maximum of 5 doses (omitting oral administration during the course). The enema must be retained and is therefore preceded by a cleansing enema and by a sedative dose of barbiturate.

Acetarsone, N.N.R. ("Stovarsol"), acetylaminohydroxyphenylarsonic acid, containing about 27.3 per cent of arsenic, was recommended against *amebic dysentery* by Marchoux, 1923, but effective doses are unsafe, toxic arsenical effects appearing in about a sixth of the patients (Anderson and Reed, 1934; Bender, 1927). It is administered by mouth, 0.125 Gm. to 0.25 Gm. (½ to 1 tablet) two or three times daily for a week; then an intermission of ten days before a second course is given. It has been tried against *syphilis*, especially for oral administration to children, but its value is doubtful. It is less effective than arsphenamine and bismuth (Pillsbury and Perlman, 1939), and is also objectionable on account of its variable toxicity (Rosahn and Kemp, 1937). Good results are reported in *Vincent's angina* from local application of 10 per cent solution, supplemented by oral administration (C. H. Maxwell, 1936); and in *trichomonas* vaginitis, from insufflation of a 12.5 per cent powder diluted with kaolin and sodium bicarbonate (G. Gellhorn, 1933). Acetarsone is a white, odorless powder, stable at ordinary temperature, of a slightly acid taste. It is slightly soluble in water, freely if alkalinized. It is marketed as tablets of 0.25 Gm.

Phenarsone Sulfoxylate, N.N.R. (*Aldarsone*), consists chiefly of the sodium salt of 3-N-methanal sulfoxylic acid amino- 4-hydroxy phenylarsonic acid, containing about 18 per cent of arsenic. Its toxicity is relatively low, but it may produce untoward effects similarly to carbarsone. It is used locally against trichomonas vaginitis by insufflation of a powder containing 0.5 Gm. of phenarsone and 2.5 Gm. of kaolin. This may be supplemented by vaginal supposition, at 0.13 Gm. Phenarsone sulfoxylate is also employed to treat syphilis of the central nervous system, especially to supplement fever therapy. It is soluble in water and is injected intravenously, 1 Gm. in 10 cc. of sterile distilled water once a week, for forty or fifty weeks.

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DRUGS USED IN AMEBIC DYSENTERY

Infection by Entameba histolytica presents interesting problems in chemotherapy. The amebae establish themselves in the lumen and tissues of the intestinal tract, and may spread to the liver and produce hepatic abscess. As with other protozoan diseases, recent infections yield fairly readily and quickly to active chemotherapy, but may relapse after a time; chronic infections are easily improved, but difficult to eradicate. *Acute dysentery* with malignant onset and course calls for prompt and energetic treatment. *Emetine*, an ipecac alkaloid, is most effective in bringing the infection under control, arresting the diarrhea and alleviating the other symptoms; but the cure is generally incomplete, as it does not kill the cysts. In chronic dysentery it is the most useful agent for the amebic hepatitis and liver abscess. The other practically effective antiamebic drugs are the phenylarsonates, carbarsone and acetarsone, and the iodohydroxy quinoline compounds, chiniofon, vioform and diodoquin. Faust, 1946, considers *chiniofon* as the best agent, more effective and less toxic than *carbarsone*, which he ranks next, to be used especially if chiniofon has not cured after two full courses. It is as effective as acetarsone and is much better tolerated. Uncomplicated *chronic intestinal amebiasis* is the most frequent type in the United States, and carriers may be treated with carbarsone (or vioform as second choice). Emetine is the best remedy in liver abscess.

The *practical evaluation of amebicidal agents* has been greatly facilitated by experimental infection of animals; at first of cats (Dale and Dobell, 1917; Sellards and Leiva, 1924) and later and better, of monkeys (Leake, 1931; Anderson and Reed, 1934). The results concord qualitatively and fairly quantitively with those of the clinic. High doses are required, which with some drugs approach or infringe on the toxic, so that the "therapeutic index" is important.

In vitro tests of amebicidal potency have proved of little value, and as with other protozoal chemotherapy, it is not certain whether the amebicidal effect is direct; at least, the potency appears much higher and more specific in the body.

Amebicidal Action.—Entamebae histolyticae in the stools of dysentery patients are quite unaffected by contact with emetine in dilutions of 1:2000 for one or two hours; and even 1:250 often fails to kill in this time (Allan, 1920). The action is slow, so that some organisms, especially of the encysted forms, are likely to survive when most have been killed. Entameba buccalis often survives on contact with 1 per cent emetine hydrochloride. However, the inefficiency may be due largely to unsuitable conditions, for in liquid media buffered to pH 6.8 to 7.2, Bishop, 1929, found Entameba coli killed by emetine 1:300,000, and histolytica by even more dilute solutions, the toxicity increasing with the alkalinity. On the other hand, it is suggestive that Dale and Dobell, 1917, found that the emetine alkaloids affected the ameba less than quinine, although quinine has much less effect on the disease. Experiments with other protozoa are little more than suggestive. Pyman and Wenyon, 1917, and Walters, Baker and Koch, 1917, investigated the efficiency of emetine and its derivatives on cultures, especially of Ameba limax. Emetine and cephaeline were about equal. Psychotrine was much inferior. Some emetine derivatives with higher alkyl esters were more efficient than emetine. Papaverine and narcotine (to which emetine is probably related chemically) also kill protozoa (Pick and Wasicky, 1915). Emetine is a fairly efficient *bactericide in vitro*, but acts slowly and is therefore useless *in vivo* (Kolmer and Smith, 1916).

Ipecac, Emetine and Cephaeline.—The value of ipecac root in the treatment of amebic dysentery has long been known, but its emetic action makes its administration difficult and it has been displaced by its most effective alkaloid, emetine. This and a related alkaloid, cephaeline, are entirely responsible for the antiamebic action (Vedder). Emetine, which is methyl cephaeline, is preferred, as it is more effective and considerably less emetic than cephaeline. It was first suggested by Vedder, 1912, and used successfully by Rogers, 1913.

Adequate doses of emetine usually cause prompt disappearance of all clinical symptoms in which it surpasses the other drugs. Failure to obtain striking clinical improvement within two days indicates that the dysentery is not amebic. The amebae generally disappear completely from the stools, but in most cases only temporarily. The most complete and permanent effects are obtained by hypodermic injection of emetine in early acute cases (Ross, 1916). For the encysted amebae of chronic cases and carriers, this must be supplemented by oral administration, which is difficult on account of the emetic action. The hypodermic injection of effective doses of emetine may produce serious side actions, especially on the heart and kidneys, so that continued treatment is distinctly dangerous and has been largely displaced by other drugs, especially chiniofon and carbarsone; but emetine has a special field in amebic hepatitis, where it is useful especially in early stages of liver abscess, and where arsenical drugs should not be used; and in severe or malignant acute dysentery, because it gives more prompt symptomatic relief than the other drugs, by which it may be followed. It is the only drug known to eradicate extraintestinal amebiasis (E. C. Faust, 1946). It should not be used against mild intestinal infections.

Toxicity.—The effective dosage of emetine seriously overlaps the toxic range (Leake, 1932); indeed, toxic phenomena occur from effective treatment in 80 per cent of the monkeys used (Dobell and Bishop, 1929). Excessive use is followed by accentuation or recurrence of diarrhea, sometimes by nausea, peripheral palsy, edema from renal damage, weakness and irregularity of the heart, most commonly auricular extrasystoles, auricular tachycardia, and disturbance of intraventricular conduction leading to dilatation of the right ventricle. The cardiac action is cumulative, increasing with repeated injections (L. J. Boyd and Scherf, 1941). The *heart muscle* shows early histologic damage, cloudy swelling, shrinking and atrophy of the muscle fibers, which may be followed by scarring. The dangers are greater in diseased subjects (Pellini and Wallace, 1916).

Local and gastro-intestinal effects are relatively mild or absent, with hypodermic injections of the ordinary therapeutic doses of emetine hydrochloride. Larger doses produce some nausea, vomiting, depression and pain. Even 0.25 Gm. in a single dose caused only persistent nausea (Allan). Cephaeline is more emetic. If emetine solution should accidentally touch the conjunctiva, it is very irritant (Blue, 1915). *Bloody diarrhea* in consequence of therapeutic hypodermic emetine injection is probably more common than was formerly supposed; it may be mistaken for recrudescence of the dysentery. Kilgore and Liu, 1917, describe several cases of children who received excessive doses under the mistaken notion that they would be more tolerant than adults. The *liver* and *kidneys* are affected later, chiefly with congestion and fat infiltration (Chopra, Ghosh and De, 1924; Rinehart and Anderson, 1931).

Toxic and Fatal Dosage.—Emetine hydrochloride is toxic for most animals, with 10 to 25 mg. per Kg., hypodermically (Leake, 1932). Clinical fatalities have occurred from about 25 mg. per Kg. (Leibly, 1930). These accidents do not seem to be connected with variability in the commercial preparations (Lake, 1918), but appear to be explained by cumulative action. Walters and Koch, 1917, found in animals that doses only $\frac{1}{10}$ of the minimal single fatal dose became fatal when repeated daily for three weeks.

Excretion After Hypodermic Injection.—Emetine appears in the urine within twenty to forty minutes; but the excretion outlasts the treatment by five to nine weeks. It must therefore form stable deposits in the body (Mattei, 1920), perhaps at the site of injection.

Intravenous injection has been tried, but Vedder rightly cautions against it. Baehrmann and Heinemann, 1913, had no bad results with 60 to 200 mg.; 300 to 400 mg. gave severe effects in a few minutes; vascular paralysis, marked dyspnea, unconsciousness, vomiting and diarrhea, slow pulse. This exceeds the fatal intravenous dose for rabbits (2.5 mg. per kilogram). The fatal hypodermic dose is much higher (20 mg. for rabbits).

Administration.—Emetine hydrochloride is injected hypodermically, one dose of 65 mg. (1 grain) daily for six days, followed if necessary by daily doses of 30 mg. ($\frac{1}{2}$ grain) for six days. The ultimate total of the course must never exceed 10 mg. per Kg. (Reed, 1934). It should not be repeated within a month. The administration should be stopped immediately if untoward symptoms occur. After the third day, it is advised to add carbarsone (except with hepatitis), 0.25 Gm. three times daily by mouth, for seven days; then rest for seven days; then change to chiniofon, 1 Gm. three times daily. Patients should be in bed for the first few days, to avoid collapse (Chopra and Ghosh, 1922). The first few injections usually suppress all symptoms, and cause the living amebae to disappear from the stools, but unless the full "course" is given, or they are followed by another amebicide, the disease is likely to return in the resistant chronic form.

Oral Administration of Ipecac.—The oral administration of adequate doses of soluble preparations of ipecac or emetine is likely to produce vomiting. The emesis often diminishes in two or three days and can be controlled by 10 or 15 minims of Tr. Opii. The vomiting may be circumvented by the use of salol-coated pills or of difficultly soluble preparations. A careful technic must be followed (S. K. Simon, 1918).

Difficultly Soluble Preparations.—Two types of these have been introduced: emetine fuller's earth adsorbate, and emetine bismuth iodide; but they are no longer used.

Iodohydroxyquinoline compounds, originally introduced as wound antiseptics, are effective amebicides, clinically and experimentally. **Chiniofon** is recommended by E. C. Faust, 1944, as more effective than carbarsone. It is believed to act on the intestinal amebae through the blood stream, although it is administered by mouth and rectum, never intravenously. It is not effective against amebic liver abscess. It usually produces watery diarrhea, but rarely other toxic effects with therapeutic doses; liver damage has been reported (Dyckerhoff, 1935), and it should not be used when liver function is impaired.

***Chiniofon,** U.S.P. (*yatren*), is a mixture of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, its sodium salt and sodium bicarbonate, containing about 27 per cent of iodine. It is soluble in about 25 parts of water, with effervescence; insoluble in organic solvents. Administered orally (not intravenously), preferably as enteric-coated tablets, 0.25 to 1 Gm. three times daily. It may be supplemented by rectal instillation of 1 to 5 Gm., freshly dissolved in 200 cc. of warm water. The combined treatment is continued for seven to fourteen days. *Chiniofon Tablets,* U.S.P.; usual size, 0.25 Gm.

Vioform, N.N.R., 5-chloro-7-iodo-8-hydroxyquinoline, also used as dusting powder for wounds, was highly recommended as amebicide (Reed, 1934), but is not used extensively (E. C. Faust, 1944). In contrast to chiniofon, it is almost insoluble in water. It is administered in gelatin capsules, 0.5 Gm. daily, for ten days. The course may be repeated after a ten day interval. About one patient in twenty has severe gastric distress, and iodism may occur, but no permanent ill effects have been reported. However, it would be unwise to use it if the liver or kidneys are diseased. It is too irritant for rectal administration.

Diodoquin, N.N.R., 5.7-diiodo-8-hydroxyquinoline, is used against intestinal amebic and Trichomonas infections. It is almost insoluble in water and is administered as tablets of 0.2 Gm., 7 to 10 tablets daily for fifteen to twenty days. The "course" is therefore longer than with chiniofon. Iodide toxiderma occurs occasionally (D. N. Silverman and Leslie, 1945).

Bismuth compounds are now but little used (Faust, 1941). James and Decks, 1925, claimed good clinical success with bismuth subnitrate. Anderson and Reed, 1934, consider bismuth valuable as adjuvant to any of the other treatments, but advise the *subcarbonate* to avoid nitrite poisoning.

Heptyl Resorcinol ("Dihydranol").—This was suggested by Faust, 1930, but it irritates the gastro-intestinal mucosa, and its effectiveness has not been determined, so that its use is not advised at present (Anderson and Reed, 1934).

Diamino Acridine ("Rivanol") was recommended by O. Wagner and by F. M. Peter, 1928, but its effectiveness was shown to be negligible by A. G. Biggam and Arafea, 1930 (Leake, 1931).

Kurchi alkaloids were introduced by Acton and Chopra, 1929, but discredited by Knowles, 1930, as relatively inefficient (Leake, 1931).

Chaparro amargosa (Simarubaceae), a Mexican plant (Castela Nickolsonii), has been used in amebic dysentery, with successful results and without bad effects. The bitter infusion is used. It kills entamebas (Nixon, 1914, 1916). It effected cures in cases refractory to emetine (Shepheard and Lillie, 1918). Sellard and McIver, 1918, isolated a product toxic to small animals, which is apparently glucosidal. They also give an abstract of the early literature. Faust, 1946, believes that "the results are not yet sufficiently advanced for critical evaluation."

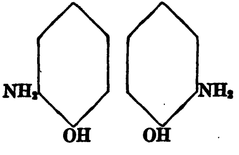
Experimental chemotherapy of rabies was attempted in mice by A. Hoyt, Fiske and Thienes, 1933, but quite unsuccessfully. The agents included organic mercurials and arsenicals, bismuth and antimony compounds, plasmoquin, optoquin, germanin, pyridium and sparteine.

THE ARSPHENAMINES

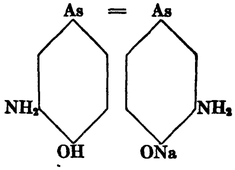
Arsphenamine (Salvarsan, 606, Arsenobenzol) and its derivatives combine a high degree of antisyphilitic action with relatively low toxicity. Various derivatives of the original arsphenamine are now used. They produce identical effects, but differences in solubility, in speed of oxidation and in toxicity are of practical significance. The arsphenamines are used with marked success in other protozoan and spirochetal infections: particularly in Vincent's angina, frambesia or yaws (Nichols, 1910), relapsing fever (Iversen, 1910), rat-bite fever and amebic dysentery (Wadhams and Hill, 1913). They appear less effective against malaria and trypanosomes, in man; and ineffective against yellow fever. Suggestive results have been reported in anthrax. They have been tried as *substitutes for ordinary arsenic,* in skin diseases, anemias, and so forth, but without great advantage. The introduction of arsphenamine accomplished a revolution in the treatment of syphilis; not the "therapia magna sterilisans" with which Ehrlich hoped to eradicate infection by a single injection; but the prompt control of the virulence of the infection, so as to stop its contagion and greatly to increase the chances of a permanent cure.

Historical.—The introduction of arsphenamine was the direct outcome of the systematic attempt of Paul Ehrlich (1854 to 1915) to combat parasites in the living tissues by chemical agents. According to Reid Hunt (U.S.P. Presidential Address, 1930) the starting point was a purely academic study of the vinyl linkage in quinine in relation to its toxicity (which led later to the development of cupreine esters against pneumonia and as wound antiseptics). In the course of this, quinine derivatives were studied on various protozoan cultures, then on trypanosomes in living animals. As quinine proved quite ineffective against these, many other agents were tried, including various arsenic compounds, first pentavalent and then eventually the trivalent arseno derivatives. The analogies of trypanosomiasis and syphilis led to the trial of the arseno-compounds against rabbit syphilis, and this culminated in "salvarsan" and the clinical cure of human syphilis. The substance was prepared by Bertheim and tested by Ehrlich and Hata. They found that a single injection of a harmless dose frees animals completely and permanently from spirillosis and certain other protozoan infections, including syphilitic spirochetes. The discovery was first described by Ehrlich and Bertheim, Oct. 10, 1909, in a German patent issued to Farbwerke Hoechst. The first scientific publication was early in 1910 by Hata, describing the trypanocidal and spirochetocidal actions. The first clinical trials were described by Alt in February, 1910, in a paper before the Magdeburg medical society. The chief report was made by Ehrlich, Hata, Schreiber and Hoppe in April, 1910, at the Congress of Internal Medicine at Wiesbaden. The first important clinical report on its use in the United States was by Nichols and Fordyce, Oct. 1, 1910, in the J.A.M.A. (review, Raiziss, 1930; the pharmacological literature was reviewed by Voegtlin, 1925).

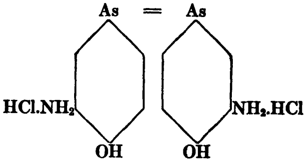
Composition.—*Arsphenamine* is the dihydrochloride of diamino-dihydroxy-arseno-benzene. The base itself (see structural formulae, below) has two amino and two phenolic groups, which confer basic and acidic characters respectively, so that the arsphenamines are amphoteric like the proteins. The addition of successive molecular quantities of an alkali, for instance, sodium hydroxide, to the dihydrochloride (*i. e.*, the commercial arsphenamine), removes first one and then both HCl groups, forming the monohydrochloride, and then the neutral base; further quantities of the hydroxide then neutralize the H of the phenolic group, yielding the mono- and then the disodium salt.



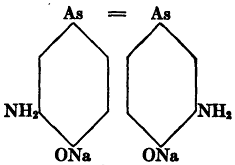
Neutral base



Monosodium salt.

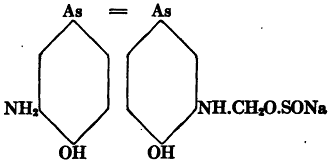


Dihydrochloride

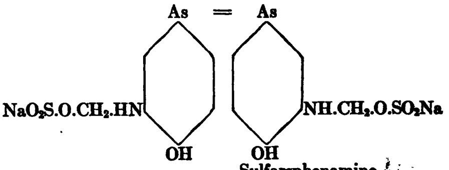


Disodium salt.

Neoarsphenamine and *sulfarsphenamine* are formed by substitution in the amido groups:

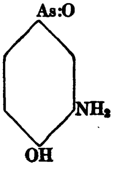


Neoarsphenamine
(arsphenamine-dimethanal-sulfoxylate)



Sulfarsphenamine
(Arsphenamine-diemethylene sulfonate).

In *trisodarsen*, NaO replaces one of the OH groups of sulfarsphenamine. *Oxophenarsine* (*marpharsen*, phenylarsenoxide, "arsenoxide," meta-amino-parahydroxy-phenyl arsenoxide),



is the first oxidation product of the arsphenamines. *Silver arsphenamine* contains silver, but its constitution is not established. It is possible that the silver is present merely as admixed colloidal metal (reference, Voegtlin). There are many other derivatives, but their present importance is slight.

Impurities.—Arsphenamine and its derivatives are so unstable that they cannot practically be prepared in pure form. The impurities vary with the method of preparation, and for the most part have not been identified. They are usually more toxic than the arsphenamines, so that it is necessary to determine the toxicity of each lot, by intravenous injection into rats or mice. Impurities may also develop on storage.

Colloidal Condition.—The arsphenamines exist in solution largely as hydrophilic colloids. They dialyze slowly; they are precipitated at the isoelectric point; concentrated solutions tend to gelatinize; they can be "salted out" by high concentrations of neutral salts (Raiziss, 1922; H. Freundlich *et al.*, 1923). The colloidal characters are especially marked with the acid arsphenamine salts, and are important as the cause of the immediate "nitritoid" and toxic reactions.

Reaction.—*Arsphenamine* (*i. e.*, the dihydrochloride) forms strongly acid solutions; its sodium salt, *i. e.*, the form which is administered therapeutically, is strongly alkaline; neutralization precipitates the insoluble base. Neoarsphenamine solutions are practically neutral. Sulfarsphenamine solutions are strongly acid. They and other derivatives formed by substitution in the amino group show a greater solubility in water through a wider range of *p*H, and have a higher degree of dispersion.

The typical *p*H of the 2.4 per cent arsphenamine salt, is for the dihydrochloride, about 2; monohydrochloride 2.7; monosodium salt, 11.4; disodium salt, 11.8 (Elvove and Clark, 1924). The isoelectric point is at *p*H 3.39 (Hunter and Patrick, 1925), but there is little ionization between *p*H 3 and 10; within this range, the base is practically insoluble. It cannot therefore exist in the blood in true solution, and even in colloidal solution only if it is stabilized by protective colloids. The acid solutions of arsphenamine have a relatively high *viscosity* which increases progressively as the isoelectric reaction is approached. The viscosity of the sodium salts is not much higher than that of water.

Oxidation is the main cause of the decomposition of the arsphenamines. The rate of oxidation varies with the access of oxygen, the temperature (Masucci, 1922) and the *p*H; and with the character of the compound. Arsphenamine hydrochloride and base are fairly stable; the sodium salts oxidize readily, the rate increasing rapidly with the alkalinity of the solution. Neoarsphenamine is unstable in the presence of oxygen, even in neutral solutions. Sulfarsphenamine in its acid solutions is more resistant to oxidation (Voegtlin and Johnson, 1922).

Absorption.—The arsenic of the arsphenamines is readily absorbed from the intestines (including the colon; Bargen, Osterberg and Mann, 1929); but probably only after decomposition. The compounds are therefore never administered by mouth.

Sojourn in the Blood.—After intravenous injection of arsphenamines, their concentration in the blood falls rapidly; clinically, for instance, the blood contained only 38 per cent of the arsphenamine immediately after the injection; this continued to fall rapidly, attaining a constant minimum in about an hour (Fordyce, Rosen and Myers, 1924). The disappearance is probably due chiefly to flocculation of the colloidal arsphenamine. Sodium cacodylate leaves the blood about as rapidly; sodium arsenate rather more slowly (d'Haenens, 1925).

Schreus and Hollaender, 1922, after the intravenous injection of 0.45 Gm., found the following concentrations of arsphenamine in the blood, by the diazo reaction, the values varying but slightly in different patients: after fifteen minutes, 25 to 33 mg. per liter; thirty minutes, 20 mg.; one hour, 13 mg.; three hours, 10 mg. In dogs at least three-fourths of the injected arsphenamines diss appeared from the blood stream within a few minute, (Kolls and Youmans, 1923); in rabbits, only one-twentieth remained in five minutes, one-thirty-fifth in an hour (Bulmer, 1923). With larger doses corresponding to 60 mg. of As, per rabbit, 99 per cent of the injected neoarsphenamine or cacodylate left the blood in ten to thirty minutes; but with sodium arsenate, also intravenously, corresponding to 60 mg. of arsenic, only 1 mg. disappeared in ten minutes, 14 mg. in thirty minutes, 38 mg. in two hours, and 50 mg. in three hours (d'Haenens, 1925). When added to blood *in vitro*, none of the arsenic passes into the corpuscles at body temperature within an hour; and only small proportions into the cells of pulped kidney, brain, muscle or heart (d'Haenens).

The **excretion** of the arsenic of the arsphenamines occurs chiefly by the bile. It is slow and incomplete, even after intravenous injection. The colloid fraction is retained longest

(F. B. Rodman, 1943). Very little is excreted unchanged.

Rate of Excretion.—Arsenic appears in the urine in a few minutes to two hours after the intravenous injection of arsphenamine (Abelin, 1911). The excretion rate is highest on the same or the next day (J. Webster, 1916) and becomes low in four days (Hoppe, 1910). Traces may be found up to three months (Heuser, 1911). After a single injection of 0.9 Gm. the urine contained less than 2 mg., the feces about 18 mg. of arsenic per day (Frenkel-Heiden and Navasartt, 1913). By the fourteenth day, the urinary level had usually fallen to 0.1 to 0.5 mg. per day (Weiss and Raiziss). The clinical urinary excretion in the first twenty-four hours for the organic arsenicals ranged as follows, in per cent of the injected arsenic (Lockemann, 1916): acid arsphenamine, intramuscular, 0.5 to 2.1 per cent; alkaline arsphenamine, by vein, 0.9 to 2.5 per cent; neoarsphenamine, by vein, 2.2 per cent; arsenophenylglycine, intramuscular, 0.1 to 7.5 per cent; arsacetin, hypodermic, 32 to 39 per cent; atoxyl, hypodermic, 88 per cent. Moderate renal insufficiency does not materially diminish the excretion of arsenic after neoarsphenamine, in contrast to the chloride and urea retention (Mathieu and Chatelain, 1926). *With repeated injections*, the excretion rises by both channels, so that nearly 60 per cent may be recovered within a week after the last injection (Underhill and Davis, 1922). The remaining 40 per cent is eliminated slowly (Mathieu, 1922). With intramuscular injections, the excretion begins more slowly and is likely to be less complete (Irokawa, 1914; Mehrtens, 1921). The excretion by rabbits is essentially similar to that of man (Burnascheff, 1912).

The *fecal excretion* of arsphenamine begins after three or four days (Underhill and Davis, 1922). It is four to ten times greater than by the urine; the difference is less marked for neoarsphenamine and for inorganic arsenicals (Pomaret, 1920; Voegtlin and Thompson, 1922; Bulmer, 1923). In dogs with permanent biliary fistula, an average of 40 per cent of injected neoarsphenamine was recovered from the bile in seventy-two hours; with oxophenarsine in forty-eight hours. Both excreted more in the first day, only traces after two or three days. Bile acids did not increase the amount excreted (J. H. Annegers *et al.*, 1944). If the common bile duct is ligated, the arsenic content of the feces is greatly lowered (Bulmer) and the toxicity and the trypanocide action is increased; ligation of the ureter increases the toxicity and potency of the pentavalent arsenicals which are excreted chiefly by the kidneys (Voegtlin, Dyer and Miller, 1922). None is excreted into the colon (Bargen *et al.*, 1929). With arsphenamine, the arsenic concentration in the bile (with dogs) may be forty times higher than in the blood (Kolls and Youmans), and thirty times higher than in the urine (Underhill and Dimick, 1927).

The *form of excretion* is not satisfactorily known (Voegtlin, 1925). A small part may be excreted unchanged, but this is doubtful. The arsenoxide-glutathione combination is tenaciously retained, while pentavalent aromatic compounds are rapidly excreted by the kidneys (Voegtlin and Thompson, 1922). From this it may be surmised that the urinary excretion occurs in the latter form. The surface tension of the urine is materially lowered (Kuroda, 1930).

The distribution has been investigated extensively in animals, after intravenous injection of the arsphenamine and neoarsphenamine. Histologic examination (obtained with reduction of silver) shows four types of localization: granular deposits in the reticulo-endothelial cells; similar deposits in the epithelium of the renal tubules and glomeruli; diffuse penetration of the mesenchymal structures, especially of the spleen; and arsphenamine emboli in the capillaries (Jansco, 1928). These localizations point to adsorption of the flocculated arsphenamines. The numerous chemical studies (Voegtlin *et al.*, 1923, rabbits; Kolls and Youmans, 1923, dogs; Bulmer, 1923, rabbits and dogs; d'Haenens, 1925, and E. D. Osborne *et al.*, 1932, rabbits; and others) show that the arsphenamine is most abundant in the organs in which the mechanical adsorption would be most extensive: in the spleen, liver and lungs and, to a somewhat less degree, in the kidneys. Arsphenamine apparently has a greater affinity for the liver, neoarsphenamine for the kidneys (F. B. Rodman, 1943).

The concentration in these organs rises soon after the injection to something like three times that of the blood. Within the first few days the concentration is higher in the spleen and liver than in the lungs; but within an hour (Bulmer) the liver begins to eliminate arsenic through the bile, and its concentration falls below the others, sometimes to a fiftieth of the spleen, on the fourth day after a single injection of neoarsphenamine or cacodylate. The lung concentration remains most constant during this period (d'Haenens). After intravenous injections of *neoarsphenamine* corresponding to 60 mg. of arsenic per Kg., into rabbits, the spleen, liver and lung together contain about a tenth of the total injected arsenic, fifteen minutes after the injection, decreasing but slightly in four days; the spleen and liver represent each about 2 mg., and the lung about 1.3 mg. of arsenic (d'Haenens). Of other arsenicals, administered intravenously in the same dosage, the *cacodylate* showed a similar distribution, but the quantity in the liver decreased more markedly, from 2.25 mg. five minutes after the injection, to 0.8 mg. in four days. *Sodium arsenate*, which would not be expected to flocculate, gave a quite different distribution. It proved fatal in two or three hours; the liver contained about 5 mg. of arsenic, double that of the other compounds; the spleen contained little, to 0.18 mg.; the lungs were intermediate with 0.35 to 0.75 mg. (d'Haenens). In a case of chronic poisoning by *arsenic trioxide*, the largest amount was also found in the liver and very little in the spleen (Underhill and Dimick, 1927), so that the latter evidently traps only the flocculated organic arsenicals. After serial injections of neoarsphenamine in dogs, which were killed by bleeding six hours after the last injection, Underhill and Dimick, 1927, found considerable individual differences in the various organs, with no direct relation to the dosage or to the number of injections. The spleen and kidneys, however, often contained more than the liver.

Other organs generally contain lower concentrations. The *bones* show perhaps the longest retention (Bulmer, 1923), but traces can be demonstrated in all the organs for months (Ullmann, 1912; Valenti, 1912; Usuelli, 1912). The *central nervous system* notably contains only traces at any time, in chronic as well as in acute poisoning, and with inorganic as well as with organic compounds; indeed, d'Haenens found less arsenic in the brain of rabbits after acute poisoning by intravenous injection of sodium arsenate than after cacodylate or neoarsphenamine. E. D. Osborne, Putnam and Hitchcock, 1932, found no appreciable amount of arsenic in the central nervous system of rabbits after arsphenamine or tryparsamide. The *cerebrospinal fluid* shows traces of arsenic within an hour after intravenous injection, in a fourth to a half of the patients, averaging 0.0036 mg. of arsenic per 100 cc. (Mehrtens and McArthur, 1919; Fordyce *et al.*, 1923). Sulfarsphenamine penetrates into the cerebrospinal fluid of rabbits much better than do the other arsphenamines (Voegtlin *et al.*, 1923). The *milk* also participates in the excretion (Caffarena, 1912); in the milk of mothers treated clinically with arsphenamine, the arsenic concentration was approximately that of the blood (Fordyce, Rosen and Myers, 1924). Traces of arsenic pass through the *placental circulation* to the fetus (Burnascheff, 1912; Underhill and Amatruda, 1923; human, Eastman and Dippel, 1933).

Oxophenarsine (mapharsen) and its related compounds also show a high arsenic content of the liver and kidneys of rabbits. Their passage into the cerebrospinal fluid is greater if the meninges are irritated, and still greater if they are infected with spirochetes (T. Hojo, 1940). Their urinary excretion is greater than the fecal (A. C. Chance *et al.*, 1945).

Chemical Transformations.—The changes the arsphenamines undergo are known only in part. The oxidation of arseno-compounds *in vitro* goes through arsine oxides to arsonic acid (with pentavalent arsenic); and the change may be reversed by reduction:

$$\begin{array}{ccccc} \text{Oxidation} \longrightarrow & & & & \longleftarrow \text{Reduction} \\ R.As = As.R & \rightleftarrows & R.As.O & \rightleftarrows & R.AsO_3H_2 \\ \text{Arseno-compound} & & \text{Arsine Oxides} & & \text{Arsonic Acid} \end{array}$$

The middle term, amino-oxyphenyl arsenoxide, oxophenarsine, briefly called "*arsenoxide*," has been isolated from the liver of animals several hours after the administration of arsphenamine, corresponding to 10 per cent of the administered arsenic; none was found in the spleen, kidneys or the serum. After administering neoarsphenamine, it was found in the kidneys, but not in the liver (S. M. Rosenthal, 1932). This compound acts more potently and more promptly on animals infected with syphilis or with trypanosomes than do the arsphenamines and the arsonic acids (Ehrlich and Bertheim, 1912). It appears probable that the arsphenamines pass through this form and that part or all of their actions are produced by this compound, although its actual concentration in the tissues appears too low to kill the spirochetes directly. Its oxidation would proceed further to the less potent arsonic acid and thence to inorganic compounds. Voegtlin has suggested that the toxicity of arsenoxides to parasites and host is due to combination with the sulfhydryl group, especially in the glutathione: $RAsO + 2HSG = RAs(SG)_2 + H_2O$, thus preventing it from fulfilling its function in the cellular oxidation-reduction system. Accordingly, the toxicity of arsenoxides is lowered if they are injected with sulfhydryl compounds, for instance, sodium thioglycollate (review, Voegtlin, 1925).

Evaluation of antisyphilitic potency on rabbits is indispensable in conjunction with the clinical trials as a qualitative and roughly quantitative index of therapeutic value. The determination of trypanocidal potency on rats (Raiziss and Severac, 1928; intraspinal, 1930) is without value for this purpose, as it does not run parallel with the antisyphilitic potency even in compounds so closely related as different lots of neoarsphenamine (Probey and McCoy, 1930).

A standardized procedure for testing antisyphilitic agents, described by Wakerlin, Lorenz and Loevenhart, 1925, determines (1) the fatal dose; (2) the "sterilizing" (therapeutic) efficiency, including the healing of the syphilitic orchitis, blood Wassermann test, and control by autopsy and by lymph node inoculation; and (3) the "prophylactic" efficiency, by intravenous injection twenty-four hours after intratesticular inoculation. Further experience with organic arsenicals and with mercurials showed a close parallelism between the prophylactic efficiency, which can be estimated on rabbits in three months, and sterilizing efficiency, which requires eight months (Wakerlin and Loevenhart, 1928). *Efficiency against neurosyphilis* appears to be a different problem. It has been studied in mice and on rabbits inoculated with spirochetes that have been passed through mice (Raiziss and Severac, 1933). Its practical value is questionable, since tryparsamide appeared to be less potent than arsphenamine and acetarsone, which is contrary to the clinical experience.

Spirocheticidal Action in Vitro.—H. Eagle, 1938, 1939, showed that treponemas from experimental syphilitic orchitis of rabbits are immobilized and rendered noninfectious by eight hours' contact with arsphenamine or neoarsphenamine, 1:250,000, or mapharsen, 1:1,000,000, concentrations, similar to those existing in the blood after clinical doses. Bismuth is also effective.

The time of contact may be greatly shortened by increasing the concentration (Kast *et al.*, 1939). The *in vitro* spirocheticidal action of arsenoxide and of bismuth compounds is not affected by removal of oxygen and is probably due to these compounds as such. Neoarsphenamine is only $\frac{1}{60}$ to $\frac{1}{25}$ as potent in the absence as it is in the presence of oxygen, so that its action is apparently due to oxidation products; arsphenamine and silver arsphenamine are intermediate; the anaerobic potency with all the arsphenamines may probably be attributed to oxidation products in the original specimen. *Sulfhydryl compounds* (cysteine, glutathione, thioglycollic acid) abolish the *in vitro* spirocheticidal action of arsphenamines, arsenoxide, bismuth and mercury almost completely. Presumably the —SH blocks the arsenical molecules so that it cannot act on the organism. Thiamine and methionine, which contain —S—, do not inhibit (Eagle, 1939). *Bacteria* in general are not very susceptible to arsphenamine, but according to Roos, 1912, it is directly germicidal to *anthrax*, even in living animals. It is ineffective in rabbits (Mejia, 1913).

In **human syphilis**, injection of the arsphenamines or oxophenarsine diminishes the spirochetes in the chancre and condylomata within a few hours, and causes them to disappear completely in twenty-four to ninety-six hours, suppressing the contagiousness of the local lesions more effectively than any other drug. A single injection of arsphenamine also produces marked and rapid improvement after the Wassermann reaction has become positive, so that the results of one administration may equal those of months of mercurial treatment. All the syphilitic symptoms regress at once, except those that have an anatomic basis. Surface lesions and ulcers are repaired with astonishing rapidity. Gummatous and periosteal lesions are usually much improved. Malignant cases, and those resistant to mercury, also cede to arsphenamine. The Wassermann reaction generally becomes negative after about five days (sometimes with a temporary exaggeration). However, the spirochetes would soon reappear and the condition would relapse, unless medication is kept up continuously for two or three years; or unless the administration is pushed energetically by massive doses. These are about as effective as penicillin, but not so safe. With *moderate doses*, "*clinical cure*," the complete and permanent suppression of the parasites (although not necessarily their complete eradication), requires early and unremitting treatment with alternating courses of the arsphenamines, and bismuth or mercury, until cautious omission of treatment is not followed by recurrence. The arsphenamine or orophenarsine *should be started as early as possible*, best in the pre-Wassermann primary stage, and should not be deferred for any reason whatever, since a few days of delay at this time may decide between success and failure. The *early treatment* should be as intensive as possible and should be kept up regardless of reversal of the Wassermann reaction. It is considered unsafe to administer arsenicals continuously over long periods, but courses of bismuth or mercury should be interpolated instead of intermissions or "rest periods" without medication, for these encourage relapses, and delay or compromise final success. "Even a few weeks of non-treatment in the first eighteen months of the disease is likely to be profoundly injurious" (Report of the American Cooperative Committee). Arsphenamine in ordinary doses should never be the sole treatment of early syphilis. Bismuth or mercury is required partly to maintain treatment between the arsphenamine courses, but probably also because they attack the parasites in directions not covered by arsphenamine. Conversely, no patient should be treated with heavy metals alone, not even bismuth; for one thing, these do not control the contagion. If the treatment was begun in the primary stage before the Wassermann reaction had become positive, and was carried out intensively and continuously, a clinical cure (nonrecurrence of any sign of the disease within two years after all treatment ceased) resulted in 86.4 per cent of the patients under continuous treatment in the clinics of the cooperative committee, and in 71.4 per cent of the patients with intermittent treatment. These figures were reduced by about 18 per cent if the treatment was started after the Wassermann reaction was positive, but before secondary lesions had developed. *Adequate treatment during pregnancy* practically prevents congenital syphilis, especially if it is started before the fifth month. In the series of Usilton *et al.*, 1938, it reduced the percentage of stillbirths by syphilitic women to half, and raised the percentage of normal babies from 16 to 65. Treatment during a previous pregnancy does not insure protection; it must be repeated. Pregnant women tolerate antisyphilitic treatment quite as well as nonpregnant (Cole, Usilton *et al.*, 1936). *Preventive treat-*

ment, before the appearance of the chancre, confuses the diagnosis and the treatment; if the latter is not energetic and prolonged, it may result in latent syphilis. Treatment for *prophylaxis*, after exposure, is unreliable. *In the late and latent syphilis* of patients who did not receive adequate treatment, and this is still a majority (Usilton *et al.*, 1938), the response to arsphenamine is much less striking, but none the less important for clinical cure (85 per cent of treated as against 25 to 30 per cent of untreated); the earlier cases respond best (Cooperative Clinical Studies, Moore, Cole *et al.*, 1932 to 1938; Stokes, 1937). Arsphenamine is much less successful against the fibrous and perivascular syphilitic manifestations, aortitis, tabes, general paresis, and the like. Presumably these are not so accessible to the arsphenamine or to its active decomposition products.

Response of the Wassermann Reaction.—Routine arsphenamine treatment renders the reaction negative in 90 per cent of the patients in the primary, and in 85 per cent in the secondary, stage; the corresponding percentages for bismuth treatment are 85 and 77 (Leri, Tzank and Peron, 1923). The early negative Wassermann reaction is not an indication of eventual cure, and the treatment must be kept up. In *latent* syphilis, the earlier the treatment is started the more readily does the reaction respond, *i. e.*, in a larger proportion of individuals (34 per cent in early latent cases, 24 per cent in late), and with fewer injections; but as regards the latter, practically all cases that become negative at all do so by the end of the first arsphenamine-metal sequence. After four months of treatment there is little or no further serologic response. If the reaction is negative, arsphenamine may turn it temporarily to positive, the "provocative Wassermann reaction," especially in early syphilis.

Spirochete Persistence.—Although clinical cure results as a rule from adequate treatment, so that all clinical manifestations are permanently suppressed, and the patients are completely noninfectious to others and may even themselves be subject to reinfection, this does not prove that all the parasites have been eradicated. Such is not the case with protozoan infections in general. Warthin, 1918, contended on the basis of histologic evidence that some of the spirochetes perpetuate themselves indefinitely after adapting themselves to the host so as to produce only slight but continued local reactions, resulting in fibrous degenerations.

The standards of treatment which have become practically universally accepted are laid down by the League of Nations Committee, 1934, and by the American Cooperative Committee, J. H. Stokes *et al.*, 1934. They include (1) the earliest possible start, in the seronegative primary stage if feasible; (2) strict supervision of mucosae, skin, kidneys and liver, to avoid toxic effects; (3) relatively heavy dosage of arsphenamines or preferably oxophenarsine in relatively rapid succession, especially at the start; (4) when moderate doses are used, persistent and continuous attack (or at least avoidance of long intervals, League of Nations), including at least 20 or, better, 30 injections of arsenicals (the first 5 to 9 being the most important), alternating in courses with 60 bismuth injections (Stokes, 1937). Bismuth or mercury should be continued for a year after all signs of the disease have disappeared. (5) Observation of the patient for at least three years; (6) spinal fluid examination at least before final dismissal.

An illustrative routine is as follows: In the first ten days, three intravenous injections of neoarsphenamine, 0.3, 0.45 and 0.6 Gm.; third to seventh week inclusive, each one injection of neoarsphenamine, 0.6 Gm.; eighth to eleventh weeks, bismuth injections; twelfth to nineteenth, A.*; twentieth to twenty-fifth, B.*; twenty-sixth to thirty-first, A.; thirty-second to thirty-ninth, B.; fortieth to forty-fifth, A.; forty-sixth to fifty-third, B.; fifty-fourth to fifty-ninth, A.; sixtieth to sixty-seventh, B.; sixty-eighth to seventy-third, A.; seventy-fourth to eighty-third, B. (*A. stands for 0.6 Gm. of neoarsphenamine; B. stands for bismuth injections.) Bismuth or mercury should be continued for a year after all signs of the disease have disappeared. *Oxophenarsine hydrochloride* or dichlorphenarsine hydrochloride may be used instead of neoarsphenamine in this sequence; making a trial injection of 30 mg. for women, 45 mg. for men, and continuing with weekly injections of 40 mg. for women and 60 mg. for men. *For prophylaxis in blood transfusions*, when syphilis of the donor is known or suspected, Kast *et al.*, 1939, urge the addition of arsphenamine or neoarsphenamine, 1:10,000 of the citrated blood, and letting the mixture stand fifteen minutes before injection.

Administration.—Most of the arsphenamine preparations are administered by vein. Intramuscular injections are effective, and are employed with sulfarsphenamine and acetylglycarsenobenzene (solusalvarsan), but most of the other compounds are too irritant. Rectal administration is unreliable. In making the intravenous injections, care must be used that none escapes into the subcutaneous tissue, since infiltration with arsphenamine (or neoarsphenamine) is painful and may incapacitate for a considerable time. *Shaking of arsphenamine* and neoarsphenamine solutions in contact with air should be avoided, since it may result in rapid oxidation with great increase of toxicity. This is particularly dangerous with neoarsphenamine and alkaline arsphenamine, but varies for different specimens

(Roth; Schamberg, Kolmer and Raiziss, 1922). The injection should be made slowly, at least two to five minutes. A few hours should have elapsed since the last meal, or this should have been light. The patient should rest for fifteen minutes after the injection and should not eat much, smoke or use alcohol for several hours, and avoid hard work for the day. He should be warned to watch for fever, digestive disturbances and skin irritation, and to remain in bed if there is marked malaise. The administration should be avoided when the patient has an acute fever or other upset.

As precaution against untoward reactions, a thorough physical examination should be made before the treatment is started, and any weaknesses adjusted. The state of health and the tolerance of the drug must be constantly watched. The patient should be specifically questioned before every injection as to his general health, colds, reactions to the previous injection (fever, digestive derangement, itching, angina). The skin should be examined for eruptions, the urine for protein, the skin and conjunctiva for icterus. Impaired organs should receive particular attention, especially the kidneys, liver, skin and cardiovascular system. Serious organic disease of these enjoins caution in the use of the arsenicals, as do also intercurrent infections and idiosyncrasy to drugs in general.

Intramuscular injections of arsphenamine and neoarsphenamine have practically gone out of use. Arsphenamine was employed as a 10 per cent neutral suspension; neoarsphenamine in the ratio of 3 cc. of water per 0.15 Gm. This yields an approximately isotonic solution. Neither drug should be injected into the subcutaneous tissue. Intramuscular injections must not be made too near the sciatic nerve, or they may cause neuritis (Kissmeyer, 1916). The absorption of arsphenamine from intramuscular injections is slow, some arsenic generally remaining at the site of injection for months (Schuebel, 1914). Neoarsphenamine is absorbed more rapidly (Ullmann, 1912, 75 to 85 per cent within a week; Swift, 1913).

Oral administration was tried in man (0.6 Gm.), and in animals, but the therapeutic effects are feeble (Schamberg *et al.*, 1916). Vomiting and diarrhea may result, but not serious intoxication (Kolmer and Schamberg, 1912). *Rectal administration* has been used (J. M. Joseph, 1918), especially for children (Araujo, 1918). A considerable amount of arsenic may be absorbed (Noeggerath and Reichle, 1921; Mehrtens, 1921), but it is not known in what form and the clinical results are unreliable (Littman and Hutton, 1924). *Subdural (spinal) injections* of arsphenamine were tried in cerebrospinal syphilis with the hope of reaching the spirochetes in the nervous system more directly, but without much result. The safest method is the injection of the serum of the patient himself, who has recently received an intravenous arsphenamine injection (Swift-Ellis, 1913; Fordyce, Rosen and Myers, 1923). Spinal injection of arsphenamine dissolved directly in serum was advocated by Marinesco and Minea, 1914, using not over 0.5 mg. of the drug. It is safer than the watery solutions, but not so safe as the Swift-Ellis method. Gennerich, 1913, and Schubert, 1914, used cerebrospinal fluid drawn from the patient for the solution of the arsphenamines. Spinal injection of watery arsphenamine solution causes severe irritation of the cord, and should not be attempted in man (Ellis and Swift, 1913; Marinesco, 1913; Swift, 1916).

Intensive massive dose arsenic methods greatly increase the speed of clinical cure in early syphilis. By introducing large doses almost continuously during a week they arrest the disease, its symptoms and the serologic reactions, so that further treatment appears unnecessary; relapses are no more common than with the ordinary method; toxic reactions are more frequent, and sometimes serious. The intensive method has no advantage in late syphilis and should be reserved for relatively acute cases (H. N. Cole, Heisel and Stroud, 1943).

Continuous intravenous drip administration of massive doses was introduced by Chargin, Leifer and Hyman, 1935, injecting 4 to 4.5 Gm. of neoarsphenamine within five days. Frequent occurrence of peripheral neuritis caused them to change to oxophenarsine, a total of 1200 mg. A smaller total tends to give incomplete results, a larger to be toxic (W. Leifer, Chargin and Hyman, 1941). All the current methods employ oxophenarsine or dichlorophenarsine.

Many *modifications* have been introduced, varying the total dosage of oxophenarsine hydrochloride from 250 to 1250 mg., the latter equivalent to 40 per cent of the maximal tolerated dose in dogs, adjusted to weight. The administration varies from slow drip (2000 cc. in seven to ten hours), rapid drip (1000 cc. in one to three hours) and multiple injections (one or more rapid intravenous injections by syringe in a small volume of solution), the frequency of injections from once a day to twice a week, and the duration of treatment from one day to twenty weeks (D. C. Elliott, Baehr *et al.*, 1941; H. Eagle, 1944). *Experiments with rabbits' syphilis* indicate that the total curative dose is not greatly influenced by the spacing of the doses, and that continuous drip is less effective than spaced injections. The toxicity, however, depends greatly on the speed and intensiveness of the treatment, and scarcely at all on the total dosage. The therapeutic index is therefore much more favorable for spaced injections (H. Eagle and Hogan, 1942). *Clinical results* also appear to be no better for continuous five day intravenous drip than for spaced methods that spread the total 1200 mg. dosage over twelve days, by daily injection of 100 mg. (D. C. Elliott *et al.*, 1941) or 2400 mg. spread over twenty weeks as forty semi-weekly injections of 60 mg. Serious reactions are much less common with the slower methods. The *Army routine* employs the forty injections with the addition of sixteen weekly intramuscular injections of bismuth subsalicylate, 0.2 Gm. in oil, extending the whole treatment to twenty-six weeks (T. B. Turner and Sternberg, 1944). H. Eagle, 1944, studied an extensive series of patients receiving about 60 mg. of phenarsine three times weekly for twelve weeks. He concludes that the therapeutic results were rather poor unless bismuth was also used; the combined treatment effected 85 to 90 per cent of "cures." The effectiveness can also be increased by combining it with fever therapy. The Cooperating Clinics of the U.S.P.H.S., 1944 (J.A.M.A., *126:* 554), conclude that the best results are obtained by using typhoid vaccine, with multiple syringe injections of oxophenarsine. They report 85 to 90 per cent of satisfactory results in primary syphilis, 70 per cent in secondary. Of the primary, 5 to 6 per cent relapsed; of the secondary, 10 to 13 per cent. A *one day treatment* by oxophenarsine and hyperthermia has been tried, but involves technical difficulty (W. M. Simpson *et al.*, 1942).

Untoward results are usually mild. They may show all the manifestations of arsphenamine therapy (see below) except nitritoid crises. Lighter reactions are rather common, even with spaced injections, but only about 2 per cent require interruption of treatment (H. Eagle, 1944). *Pregnancy* is not a contraindication. The *milder reactions* include nausea, vomiting, diarrhea, often some fever. Almost all patients develop significant but transient changes in the electrocardiogram, especially of the T wave, during or shortly after the treatment. These are not observed with the smaller doses of the older therapy (A. J. Geiger *et al.*, 1942). Secondary anemia may develop late (J. F. Sadusk *et al.*, 1942). The series of D. C. Elliott, Baehr *et al.*, 1941, showed no evidence of significant damage to the liver or kidneys; no exfoliative dermatitis; exceptional mild and transient neurites. The series of H. Eagle, 1944, with triweekly injection, records serious reactions, chiefly jaundice, in 0.8 per cent of the patients. *Fatalities* are generally due to hemorrhagic encephalitis and rate 0.25 to 0.5 per cent for intravenous drip; Cooperative Clinics, 1944, 0.02 to 0.08 for spaced injections (H. Eagle, 1944; T. B. Turner and Sternberg, 1944), and only 0.005 per cent for the older dosage (J. H. Stokes, 1942).

The excretion of arsenic during intravenous drip administration of oxophenarsine to dogs shows that 27 per cent of the daily dosage occurs in the urine, 35 per cent in the feces (H. J. Magnuson and Raulston, 1941).

Other treponemal diseases successfully treated by arsphenamine are frambesia, Vincent's angina, gangrenous balanitis and recurrent fever. In *frambesia* (yaws) the treatment and results are the same as in syphilis, both for neoarsphenamine and for bismuth (G. M. Saunders, 1937). *Vincent's angina and gangrenous balanitis* are promptly arrested by intravenous injection of neoarsphenamine, 0.3 to 0.4 Gm. The pain disappears in a few hours, and the inflammation subsides within a day. A second injection is rarely needed. Dry neoarsphenamine or arsphenamine dusted on the lesion is also effective; or painting with a 5 or 10 per cent solution of arsphenamine or neoarsphenamine in glycerin, at first twice a day, then daily (C. Barker, 1922). Intravenous injection is used in *treponemal pulmonary gangrene.*

Nontreponemal diseases in which more or less successful results from arsphenamine have been reported include malaria, intestinal protozoan infections, kala-azar, filariasis, anthrax, lichen ruber planus, lupus erythematosus. It proved *ineffective* in experimental trichinosis, as did also antimony and various other agents (J. J. Miller *et al.*, 1932).

Tertiary malaria is checked by oxophenarsine and arsphenamines; they have little effect on plasmodium species other than vivax. In *therapeutic malaria,* neo arsphenamine, 0.15 Gm. by vein, averts the paroxysm, but it must be repeated for two or three days. It cannot take the place of quinine for permanent arrest (C. W. F. Winckel, 1941). In *clinical vivax malaria,* oxophenarsine hydrochloride, 40 mg. by vein, may be used to increase the effect of quinine in resistant cases; it has little effect alone (W. H. Stewart, 1945).

Other Metals against Syphilis.—The usefulness of mercury, bismuth (and of iodide) is discussed under these headings. *Gold* was credited with some value by Fracastor (1530) and by many later writers, especially by Chrestien of Montpellier, 1811. Legrand of Amiens, in 1836, wrote a book on it, in which he claimed it to be more effective than mercury. A reaction against mercury was in vogue at that time and a number of other metals were credited with antisyphilitic effects: *Silver* by Serres, 1836; *platinum* by F. Hoefer, 1840; *iron* by Horn; *copper* by J. R. Koechlin; *zinc* by J. H. Hancke; antimony, lead, manganese, graphite by others. Arsenic was tried early, with and without mercury, but was feared and not used widely.

Systematic chemotherapeutic studies by modern methods led to the introduction of *bismuth* by Levaditi and Sazeran, 1920. Levaditi, 1931, also tried some thirty other metals against rabbit syphilis, spirillosis and trypanosomes. As, Hg, Bi, Te, Va, Pt, Au were found more or less effective; Sb, Se, Th, Pb, Ir and the others appeared ineffective. The *malaria treatment* of paresis was introduced by Wagner von Jauregg, 1920.

Toxic and Side Actions of the Arsphenamines.—The slow *intravenous injection* of the usual solutions does not give rise to notable local phenomena. There is sometimes intense but fleeting pain in the shoulder, possibly from endocardial irritation. A peculiar disagreeable odor and taste of garlic, ether, suet or strong peppermint candy is also often perceptible for a short time. There may be nausea, and sometimes vomiting, to be treated by gargling with cold water. Injection of solutions of arsphenamine or neoarsphenamine into the *subcutaneous tissue* produces severe burning pain, followed by painful irritation for several days. With acid and alkaline solutions this is due partly to the reaction, partly to the arsphenamine; acid arsphenamine causes severe and persistent pain; alkaline solutions of arsphenamine may produce corrosion, ulceration and gangrene. Neutral suspensions of arsphenamine also result in severe but slower irritation, and the absorption is incomplete (H. E. Robertson, 1913). *Neoarsphenamine* solutions, although neutral, produce severe inflammation, infiltration and fibrosis, which may proceed to abscess. If an injection should accidentally be made into the subcutaneous tissue, it should be aspirated and promptly diluted by injecting 10 to 20 cc. of normal saline solution into the site (Dietel, 1925). Thiosulfate solution, which is often used, acts similarly and appears to have no material advantage.

Intraperitoneal injection of neoarsphenamine into rabbits produces transient aseptic peritonitis, but no permanent injury, and is completely absorbed (W. Rosenberg, 1924). The incidence of adhesions is greatly reduced by adding 1 to 4 per cent of sodium bicarbonate to 1 per cent neoarsphenamine (B. G. Noble, 1929).

Toxicity by Mouth.—Neoarsphenamine, 0.3 Gm., has been taken by mouth for six successive days, with no other effect than some temporary gastric discomfort and diarrhea. The *Wassermann reaction* remained positive (M. Friedmann, 1920).

Toxic Frequency, Danger and Precautions.—Some degree of systemic reactions occurs in ½ to 15 per cent of all injections. They are annoying and alarming, but not often dangerous. The danger may be minimized by using reliable drugs; exact technic of preparation and administration of the solutions; and painstaking surveillance of the patient as described under administration.

American Statistics.—The data of Cole, DeWolf *et al.*, 1931, represent a uniformly supervised series, with conservative doses of arsphenamine and neoarsphenamine, which gave approximately equal incidence; and a smaller number of other arsenicals, of which sulfarsphenamine appeared to be distinctly more liable to serious complications. The entire series comprised about 78,000 injections on 1200 patients; nearly all the patients were under treatment for six months or longer. Toxic effects or complications were observed in 1:123 injections. The most common occurred in the following order of frequency: severe gastro-intestinal reactions, 1:700 injections (in round numbers); slight skin eruptions, 1:1000; pruritus, 1:1500; nitritoid, 1:1900; crustaceous and exfoliative dermatitis, 1:3000; icterus, 1:3500; death, 1:6500; the latter included: hemorrhagic encephalitis, 1:13,000; exfoliative dermatitis, 1:15,000; and hepatitis, 1:78,000. Nearly two-thirds of the patients had a single complication; a fourth showed two; an eleventh, three. Patients oversensitive to one arsenical are probably so to all. Arsphenamine and neoarsphenamine gave essentially the same percentage of toxic reactions, but purpura and hemorrhagic encephalitis were more common with sulfarsphenamine, as noted also by Stokes and O'Leary. The frequency of toxic effects is somewhat greater for women; Negroes rather less than white. Age is important, the toxicity being generally highest above forty years and lowest below twenty years; but encephalitis and exfoliative dermatitis are more frequent in young adults. Twenty-one deaths from arsphenamines were reported from New York City in 1937.

Physical (*Colloidal*), *Chemical* (*Arsenical*) *and Indirect* (*Immune*) *Factors.*—The *immediate and early reactions* are due mainly to *physical interactions* between the colloidal particles of the arsphenamine and of the tissues. They are therefore confined essentially to the intravenous injections, and vary quantitatively with the colloidal instability of the solutions. They are by far most serious with acid arsphenamine, much less with alkaline arsphenamine, slight and rare with neoarsphenamine, and practically absent with oxophenarsine. They should be avoided by dilution and slow injection, by stabilization of the colloids, or by selection of the more stable compounds.

Delayed reactions are partly chemical, owing to the formation of more toxic arsenic compounds or to the injurious effects of the products of the destruction of parasites, and of accompanying *immune reactions.* Too little is known about either of these to permit a sharp classification.

Immediate "nitritoid" reactions (angioneurotic symptom complex), due to flocculation or agglutination of the blood by the colloid arsphenamines, bear a general resemblance to vasodilatation ("vasoparesis"); the milder grades to nitrite action; the severer grades to anaphylactic reaction (Swift, 1912). The *symptoms* start during or within a few minutes after intravenous injection, with a burning ethereal taste; flushing of the face; injection of the conjunctiva; edema of the tongue and eyelids; anxiety, nausea and vomiting; then profuse perspiration. Cough, dyspnea, cyanosis and precordial distress are sometimes present. The pulse is full at first, then weak, with a pallid skin. In severe cases there is unconsciousness, with scarcely perceptible pulse. Occasionally there are attacks of severe lumbar pain during the injection. These symptoms may disappear in one-quarter to one-half hour, or they may be followed by later symptoms (Schamberg *et al.*, 1917). The immediate symptoms are rarely dangerous; even actual collapse (which is said to be more frequent after the second dose) usually ends in rapid recovery, rarely in death (Tomasczewski, 1913). The occurrence of the immediate reactions does not preclude continuance of arsphenamine therapy, but renders it advisable to use oxophenarsine, which is not liable to nitritoid reactions; although an exceptional case of severe crisis was reported by A. L. Shapiro, 1945.

These "reactions" occur in 0.05 to perhaps 5 per cent of the administrations of alkaline arsphenamine; the relative frequency depends mainly on the conditions of administration, especially on giving the drug with the stomach empty, and having the patient rest for an hour or more after the administration. The rate of injection and the proper alkalinization, are also important factors A few patients react even with the most careful technic,

Treatment of Nitritoid Reactions.—The injection should be stopped with the first sign of flushing. If the reaction does not subside immediately, epinephrine should be administered hypodermically, ½ cc. of 1:1000. This usually gives prompt relief, but if necessary, it may be followed by 0.1 to 0.15 cc., well diluted, by vein. Once recovered, the patient does not relapse. With those who tend to react to each injection, epinephrine may be used as a preventive, 0.25 cc. of 1:1000, hypodermically. Patients hypersusceptible to arsphenamine are sometimes also hypersusceptible to epinephrine, the effects of which may be as alarming as those of arsphenamine (Stokes, 1919; Cole).

Effects on Circulation.—The rapid injection of arsphenamine solution into the femoral vein of dogs produces a gradual but severe and persistent fall of blood pressure, *i. e.*, a shocklike state (Auer, 1911). This is preceded by rise of the pressure in the pulmonary artery (Jackson, 1923; Jackson and Raap, 1920) and dilatation of the right heart and swelling of the splanchnic organs (Jackson and Smith, 1918). The rise of the pulmonary pressure indicates that the actions are due chiefly to increased resistance in the pulmonary circulation; the heart is also depressed directly (Auer, 1911; Luithlen, 1913) as well as by the fall of coronary pressure; but the rise of the pulmonary pressure indicates that the cardiac impairment plays a secondary role. All these effects are diminished if the arsphenamine is much diluted, or if it is injected slowly, and they are slight if it is injected into the portal vein or into the femoral artery. The effects are greatest for acid solutions of arsphenamine, and least for strongly alkaline solutions. They are slight for neoarsphenamine and sulfarsphenamine, strong for silver arsphenamine (Jackson and Raap, 1920).

The reactions parallel the colloidal properties of these substances. Voegtlin, Johnson and Dyer, 1924, observed a direct correlation between the changes of toxicity and viscosity; for instance, warming alkaline arsphenamine solution, under conditions that preclude oxidation, decreases the toxicity (Hunt, 1921), with a corresponding decrease of viscosity. The less dispersed, more viscid and more coagulable colloid compounds tend to produce flocculates, precipitates or agglutinates with the blood, which would obstruct the nearest capillaries; *i. e.*, the pulmonary capillaries if the injection is made into a systemic vein (Joseph, 1911). This embolism cuts off a part of the pulmonary circulation and so causes the rise of pressure in the pulmonary artery and fall of pressure in the systemic arteries, which is the characteristic of the shock in animals and of the "nitritoid reactions" in man. The arsphenamines do not act on the muscle of the pulmonary vessels (Busacca, 1924); the systemic vessels of frogs are constricted (Luithlen). If the injection is made into the portal circulation, the pulmonary obstruction does not occur because the emboli are filtered out and broken up before they reach the lung; with injection into the femoral artery, this occurs in the leg. The phenomena are analogous to those of fat embolism. With dilute solutions, or slow injections, or with the more stable colloids, the precipitates are so scanty and dispersed that they can be washed through the capillaries without notable disturbance (Joseph, 1911).

Interaction of Arsphenamine and Blood.—Precipitation by mixing acid arsphenamine and serum can be demonstrated in the blood vessels as well as in the test tube (Joseph, 1911). Alkaline arsphenamine is much less precipitant, but there is at least a tendency to flocculation (Danysz, 1917), which varies perhaps with different bloods, as was claimed by Berman, 1918. The precipitates contain both arsphenamine and protein. Since arsphenamine is practically insoluble at the *p*H of the blood, it would necessarily be precipitated unless it is kept in colloidal solution by protective proteins. In alkaline solutions these would be formed by the action of the alkali (Oliver and Douglas, 1923), thus explaining the difference in precipitation. The protein precipitation by acid solutions may be due partly to adsorption, partly to the flocculent effect of the phenolic group of the arsphenamine. It may be recalled that the intravenous injection of phenol also produces shock phenomena (Pomaret, 1923). The characters of the proteins that remain in solution are also altered; fibrinogen, for instance, is rendered noncoagulable by thrombin, so that *arsphenamine prevents the coagulation of blood*, both *in vivo* and *in vitro* (Oliver and Douglas, 1922). Neoarsphenamine and sulfarsphenamine produce this effect only with doses much larger than the therapeutic (Anwyl-Davies and Mellanby, 1923). Arsphenamines alter the properties of the *blood corpuscles*, so as to produce agglutination, *in vitro* and *in vivo* (Oliver and Yamada, 1923). The importance of these in the lung embolism of acute fatalities was shown by Karsner and Hanzlik, 1920. Necropsy from fatal injection of *acid arsphenamine* shows ring-shaped hemorrhages widely spread in the white matter of the brain, which are attributed to embolism by agglutinated erythrocytes (G. C. Parker and Perkins, 1940).

Protection by Hydrophilic Colloids.—The agglutinating and anticoagulant effect of the alkaline arsphenamine may be prevented by the previous addition of hydrophilic colloids, as by mixing the arsphenamine solution with serum (Kritschewsky, 1921); or more practically with gelatin (Oliver and Yamada, 1922). These reduce the toxicity greatly (Oliver, Yamada and Kolos, 1923; Roick, 1915).

Hemolytic Action.—Alkaline arsphenamine solutions hemolyze slowly, by their alkalinity; acid solutions, or isotonic neutral solutions of neoarsphenamine, are not hemolytic (Corridi, 1912).

Leukocytes.—Arsphenamine injections are followed by leukopenia, and after several hours by leukocytosis, especially of neutrophile polynuclear cells (Tunnicliffe, 1922).

Excised Organs.—The effects were studied by Joseph, 1911 (skeletal muscle); Peruntz and Rosemann, 1923 (intestines); and Busacca, 1924 (autonomic system).

Sensitization by Repeated Injections.—If arsphenamine injections are repeated at intervals of several days to two weeks, the toxicity appears sometimes to be considerably increased (Flandin and Tzanck, 1921; Busacca, 1923; Launoy, 1923); but the result is uncertain (Berman, 1918), and it is doubtful whether it is analogous to ordinary anaphylaxis (Kolle *et al.*, 1920).

Early and delayed toxic reactions are common. They start within one to four hours, with a chill and *febrile symptoms*, headache, nausea, vomiting and diarrhea of varying severity. The temperature is usually between 100° and 102° F. Occasionally there are severe pains in the legs or back; sometimes polyarthritis (Tzanck *et al.*, 1936). These reactions need not cause alarm (Ormsby, 1917) and do not demand interruption of the arsphenamine treatment. They occur especially in the presence of infections even if slight (Wechselmann, 1910). The symptoms usually recede in twelve to twenty-four hours, leaving some lassitude and weakness. More rarely, the temperature, vomiting and diarrhea may continue for several days. In some cases, the urine is scanty and contains albumin and casts (Schamberg *et al.*, 1917).

The fever is generally attributed to the products of the massive destruction of spirochetes (Neisser, 1910), It may also result from pyrogenic water (Wechselmann: 1911). Various other explanations have been proposeds Ehrlich's, that the bacterial products sensitize the tissue to arsenic; Yakimoff, 1912, a colloidoclastic react on between the bacterial proteins and arsphenamine; Luithlen and Mucha, 1913, destructive action of arsphenamine on pathologic tissues.

Herxheimer reactions are exacerbations of the local syphilitic manifestations, usually in secondary or late syphilis, which may follow the first few injections. They are attributed to liberation of the treponemal endotoxins. They are harmless in the secondary stage; in tertiary syphilis they may be dangerous if vital organs are affected. They are prevented by starting the treatment with one or two small doses (0.15 Gm. of neoarsphenamine) or by a preparatory course of bismuth or mercury.

Kidney Involvement.—A few casts and a trace of albumin are not uncommon on the day after the injection, and the phthalein output may be somewhat diminished, the blood urea a trifle increased (J. A. Elliott and Todd, 1920). This renal impairment is generally temporary and has little significance. It does not demand interruption of the treatment unless the albumin or casts persist. In that case, the arsphenamine (and mercury or bismuth) should be stopped until the renal irritation has disappeared and then be resumed with great caution. Serious nephritis develops especially in connection with the skin lesions, but sometimes also independently.

Marasmus.—Occasionally the arsphenamine appears to lower the general health, without definitely ascertainable cause. In such case, it is generally advisable to discontinue the administration until the health has been restored. Anemia has been described by Moore and Keidel, 1921. Ordinarily, the blood picture is not changed, even in chronic intoxications (rabbits, Herzog and Roscher, 1923).

Metabolism.—The effects resemble those of arsenic (Postoiev, 1912). Syphilitic patients, under treatment, show some nitrogen loss on the day after the injection; otherwise the changes are inconstant (Cappelli, 1911).

Exanthemata.—Rather exceptionally, various types of skin eruptions, ranging from mild to dangerous exfoliative, may appear in a few hours to several days, generally accompanied by renal irritation. The more common types are patches of urticarial, scarlatinoid and morbilliform erythemas; herpes; or rarely purpura (Labbe and Langlois, 1919). Sometimes there is only itching. The eruptions generally subside in a day or two. They do not absolutely contraindicate continuation of the arsphenamine treatment, but it may be advisable to go slower. Recurrent urticaria may be prevented by changing to oxophenarsine, or by prophylactic injection of epinephrine, 0.5 cc. of 1:1000, hypodermically, five minutes before the arsphenamine. Persistent pruritus usually turns into severe dermatitis if the injections are continued. Sulfarsphenamine sometimes induces purpura hemorrhagica and occasionally aplastic anemia.

Dermatitis may develop in one to fourteen days. It takes various forms and may turn into exfoliativa, the latter generally with severe nephritis, with slow recovery, and often with fatal outcome (J. E. Moore and Keidel). These severe effects are probably direct arsenic actions. If there is vesication, exfoliation or marked and persistent itching, arsenical treatment must be permanently abandoned.

Sodium thiosulfate is often injected in treating the dermatitis (Ravaut, 1920), 1 Gm. in 10 cc. of water intravenously, daily or on alternate days, for one or two weeks; sometimes supplemented by oral administration of 1 Gm. in water, three times daily. Its value is questionable (Voegtlin, 1923).

Whatever action it has is probably on the dermatitis rather than on the arsenic; for it does not decrease the toxicity of arsenoxide (Voegtlin) and scarcely at all that of sodium arsenite or arsenate; *i. e.*, it does not protect against superfatal doses, and only partly against just fatal doses. It appears rather to decrease the urinary elimination of the arsenic, but this has no relation to the improvement of the dermatitis (A. G. Young, 1928). It causes some decrease in the trypanocidal efficiency of arsenicals, *in vivo*. The action has been attributed to the formation of colloidal arsenous sulfide (Kuhn and Loevenhart, 1925).

Severe Late Intoxications.—Occasionally, severe and even fatal reactions set in three days to several weeks after administration, with phenomena referable either to the kidneys or skin, or to the brain or liver. They may be due to direct actions of the arsphenamines, or to the inorganic arsenic compounds formed from them; and to special susceptibility to either.

Parenchymatous Degeneration.—Fatty and necrotic changes are of inconstant occurrence, clinically and in animals. They resemble ordinary arsenic lesions, and involve especially the liver (acute yellow atrophy); then the kidneys, heart, nervous system (encephalitis hemorrhagica) and spleen (Morel *et al.*, 1912). Mucha and Ketron, 1912, claimed that even small doses damage the renal vessels and glomeruli. The intestines may also show hemorrhagic and inflammatory changes (Saccone, 1912). The lesions occur especially after repeated injection, and are increased by mercury, uranium, epinephrine or roentgen treatment (A. Loewy and Wechselmann, 1913). Luithlen, 1913, emphasized the greater toxicity of arsphenamine to animals subjected to these vascular injuries, and believes them analogous to the Herxheimer reaction; *i. e.*, that this is a specific effect on vessels previously injured by the luetic process. In a series of *phenylarsenoxides*, the systemic toxicity was found to parallel the amount bound by the red corpuscles, liver and kidneys, *in vivo*, and inverse to the rate of excretion (R. B. Hogan and Eagle, 1944).

Hepatitis.—Rather exceptionally, the syndrome of jaundice, generally accompanied by fever, may appear from three days to several weeks or even six months after treatment. It occurs usually only after one or two courses of intravenous injections. It is less frequent with oxophenarsine than with neoarsphenamine. Its incidence is higher when epidemic hepatitis prevails. The symptoms start with sudden intense icterus. Most cases recover in a few days to three months (Wosegien, 1923); others run rapidly to a fatal ending, with vomiting, hemorrhagic phenomena in the viscera, tubular nephritis and the general typical symptoms and autopsy findings of acute yellow atrophy (Severin and Heinrichsdorf, 1912). The hepatitis is probably caused directly by the arsenical, for icterus was rarely observed in syphilis before arsphenamine was introduced; it has occurred from the use of the drug in nonsyphilitic conditions (Filliol, 1930). When icterus appears, arsenical treatment should be discontinued. In severe cases the diet should be light or liquid; fluids should be forced, and a saline cathartic administered. Caution should be used when resuming the arsenical, as is usually advisable especially in early syphilis.

Diet on Incidence of Hepatitis.—Dogs are susceptible to arsphenamine and oxophenarsine hepatitis. The susceptibility is increased by diets poor in meat protein or by abundance of fats. They are protected by carbohydrates, and especially by high protein diets (not by casein) and by feeding methionine or cysteine (W. J. Messinger and Hawkins, 1940; J. P. B. Goodell *et al.*, 1944). The effect was also noticeable, but not very significant, in clinical postarsphenamine jaundice (R. A. Peters *et al.*, 1945).

Hemorrhagic purpura is not uncommon with sulfarsphenamine, and is relatively rare with the others. It may develop twenty-four to forty-eight hours after the injection. If it is severe, it may be necessary to abandon arsenicals.

Polyneuritis is infrequent and may be syphilitic rather than arsenical. *Optic neuritis* is a rare sequel of arsphenamine and neoarsphenamine. It is generally classed with the neurorecurrences; but Arganarez, 1914, reported a series of cases which he attributed directly to the drug and not to the spirochetes. *Optic lesions* in animals require much larger doses than those concerned in clinical amblyopias. With rabbits, they require the presence of an amino group in the para position. They occur both with tri- and pentavalent arsenic; but they may be made more intense with the pentavalent, because their lower systemic toxicity permits larger doses (A. G. Young and Loevenhart, 1923).

Hemorrhagic encephalitis is a rare but most dangerous reaction. It occurs especially after large doses, or when ordinary doses are given in close succession. It is more frequent in young adults. The symptoms begin in two to four days, with headache, weakness, vomiting, muscular twitching, epileptiform convulsions, suppression of urine, dilatation of pupils, absence of reflexes, coma and death within three or four days, generally in a few hours after the onset. Paralytic symptoms may be observed (Chiari, 1913). The necropsy generally shows edema of the brain or hemorrhagic encephalitis; often also degenerative parenchymatous changes in the kidneys, liver, heart muscle, spleen, and so on. (Busse and Merian, 1912; Corlett, 1913). The encephalitis appears to be more frequent with sulfarsphenamine. It is probably a direct arsenical action, for similar phenomena may be observed in nonluetic patients (Lube, 1914), and in animals (Marschalko and Veszpremi, 1912). It is not inconceivable, however, that some cases may be Herxheimer reactions (Laredde and Jamlin, 1914).

Neurorecurrences.—Severe nervous manifestations sometimes follow arsphenamine injections after an interval of weeks or months, by epileptiform convulsions; acoustic, more rarely optic, facial and other neuritis. These do not appear to be due to the arsenic, for similar effects may occur in mercurial treatment, and they recede on further arsphenamine or mercury medication. The explanation of Ehrlich, 1911, is generally accepted, that they are caused by the incomplete destruction of the parasites, those which escape being then less exposed to the normal restraining influences, and assuming a greater virulence. Their occurrence calls for more vigorous arsphenamine medication.

Choice of Preparations.—The trend of clinical practice is toward oxophenarsine hydrochloride (mapharsen), or the dichlorophenarsine hydrochloride, which forms oxophenarsine in the body. These can be marketed as practically pure preparations which keep well, especially the dichlorophenarsine, while arsphenamines contain or form derivatives, which are often more toxic and must be limited by bio-assay. Therapeutic results with oxophenarsine are fully as good as with the arsphenamines; nitritoid reactions are absent; other toxicities are about the same. Of the arsphenamines, neoarsphenamine is used five or ten times as often as all the others combined (H. H. Hazen, 1929). It is preferred especially in general practice chiefly because its administration is much simpler, and less liable to acute fatalities from errors of technic. Although somewhat less potent than the old arsphenamine, which is therefore preferred by some specialists, it is sufficiently effective in practice. The other arsphenamines—sulfarsphenamine, trisodarsen—represent rather superficial modifications which still have a somewhat experimental status. Sulfarsphenamine can be administered intramuscularly (Stokes and Behn, 1924). Silver arsphenamine and bismarsen are attempts to combine metals which it would seem better to give separately as circumstances may indicate. *The clinical valuation of antisyphilitic agents* is discussed by H. N. Cole, 1938. In general, they are best compared in early syphilis, as the effects are then most definite.

Comparison of Arsphenamine and Neoarsphenamine.—Arsphenamine gives an acid solution which requires careful alkalinization or serious and fatal accidents ensue; neoarsphenamine forms a neutral solution with water, which can be injected directly. It is not hemolytic in ordinary clinical solutions, but only when very dilute or very concentrated; arsphenamine hemolyzes with practically all concentrations. Arsphenamine is less oxidizable in air and forms more stable solutions, and gives more uniform and prompt therapeutic results.

The data compiled by A. B. Cannon and Karelitz, 1931, showed that old arsphenamine averaged about a third fewer injections than neoarsphenamine to accomplish the healing of primary and secondary lesions and to reverse the Wassermann reaction, and the percentage of relapses was only an eighth as great. Toxic reactions of all kinds were at least as frequent with the neoarsphenamine (Pearce and Brown, 1917).

Ascorbic acid, when added to arsphenamine solutions, decreases their toxicity and prevents the increase of toxicity on standing (J. Dainow, 1939) by retarding their oxidation of the o-aminophenol (McChesney, 1945). H. N. Bundesen *et al.*, 1941, confirmed that this extends also to neoarsphenamine and oxophenarsine; the proportion of one part of ascorbic acid to three of the arsenical inhibits the toxic oxidation for a week and suppresses the patch test. E. W. McChesney *et al.*, 1944, showed that injection of ascorbic acid also protects against the toxicity of neoarsphenamine. The effect is greatest if the two are mixed, but some protection occurs if they are injected at different sites. The therapeutic efficiency does not appear to be decreased. Para-aminobenzoic acid and some other organic acids also confer protection.

Preparations.—Oxophenarsine Hydrochloride, U.S.P., *Mapharsen*, "*arsenoxide*," the hydrochloride of 3-amino-4-hydroxyphenylarsine oxide, containing about 31 per cent of trivalent arsenic; a white powder soluble in water, alkalis and acids. Usually distributed in air-free ampuls with buffering agents and other substances to render its solution compatible with human blood. It should not be stored longer than two years. Discolored solutions should not be used. Average dose, 45 mg. dissolved in 10 cc. of water and injected rapidly by vein. The solution as buffered contains oxophenarsine base. It is not precipitated by mineral acids (difference from neoarsphenamine) or by alkalis (difference from arsphenamine). It appears that the actions of the arsphenamines are due to their oxidation to this substance in the body (Rosenthal and Probey, 1933). When it is injected directly into syphilis-infected animals and patients, it appears fully as effective as arsphenamine, and acts much more promptly (Tatum and Cooper, 1934; Gruhzit, 1935). The treponemas disappear from the open lesions in less than twenty-four hours. Originally it was considered too toxic for therapeutic use, but in proper dosage (which is about a tenth that of arsphenamine) it is probably safer than the arsphenamines since it is a definite and uniform chemical substance and does not flocculate with plasma protein. No nitritoid reactions have been reported (E. A. Levin and Keddie, 1942). Only six fatalities had been reported for some twelve million injections by the ordinary routine (G. D. Astrachan and Cornell, 1943).

The *fate of oxophenarsine* was studied by H. N. Wright *et al.*, 1937, for intravenous injections on rats; fifteen minutes after the injection 34 per cent of the total arsenic was recovered from the skeletal muscles, 22 per cent from the blood, 12 per cent from the kidneys and 7 per cent from the liver. Two hours later, the blood content had fallen to 7 per cent, but that of the other organs was not greatly changed. With three injections per week for two to ten weeks there was but little retention and therefore little opportunity for cumulation.

Dichlorophenarsine Hydrochloride, U.S.P. (Chlorarsen phenarsine), the hydrochloride of 3-amino-4-hydroxyphenyl dichlorarsine, containing about 26 per cent of trivalent arsenic; a white powder, soluble in water, alkalis and dilute mineral acids. Usually in air-free ampuls as a mixture analogous to oxophenarsine. It is more stable than oxophenarsine, but should not be stored longer than three years. It is transformed to oxophenarsine when it is dissolved in water and acts as such. It is usually distributed with buffering agents. Dosage, as for oxophenarsine. Animal experiments and clinical studies were reported by R. R. Tompsett *et al.*, 1941.

***Neoarsphenamine, U.S.P.**, a product obtained by the action of sodium methanal sulfoxylate on arsphenamine, consists chiefly of sodium 3, 3′-diamino-4, 4′-dihydroxyarsenobenzene methanal sulfoxylate. It contains about 20 per cent of As, two-thirds as much as arsphenamine, and the dosage accordingly is 50 per cent higher. Neoarsphenamine is distributed in air-free ampuls. A yellow powder, readily oxidized on exposure to air, becoming darker and more toxic. Very soluble in water. Solutions of neoarsphenamine must be freshly prepared when required for use, using 2 cc. of cold distilled water per 0.1 Gm. of neoarsphenamine. This gives a neutral 5 per cent solution. It should not be shaken, and should be injected immediately to avoid toxic oxidation. The intravenous injection should not take less than five minutes. Average *dose*, 0.45 Gm. The ampuls should be stored in a cool place. The commercial ampuls contain the usual dosages. "The ampule containing the drug is immersed in alcohol; then carefully wiped off; the neck filed across and broken off; and the contents sprinkled on the surface of cool, sterile distilled water and allowed to dissolve *without shaking* the solution. Any product incompletely soluble should be discarded. Solutions of neoarsphenamine must be injected *immediately* after their preparation. Neoarsphenamine must not be warmed and the temperature of the injected fluid should not be more than 20° to 22° C. (68° to 71.6° F.)." "The drug may undergo deterioration in the ampule, and care should be exercised to use the drugs of normal color and free solubility"—N.N.R. (G. B. Roth, 1922). *Peritoneal injection* of neoarsphenamine has been used in infants with congenital syphilis; it appears to be effective and fairly safe (Grulee *et al.*, 1928).

Arsphenamine, U.S.P. (3, 3 diamino 4, 4 dihydroxyarsenobenzene dihydrochloride), contains not less than 30 per cent of As. A light yellow powder; odorless, or slight odor; hygroscopic. Oxidizes on exposure to air, becoming darker and more toxic. Sol. in water, alc. and glycerin. Marketed in sealed glass containers, free from air, containing the ordinary doses. Dose, *Caution!* Intravenous, 0.3 Gm.; less for debilitated patients. The first test dose should be of 0.2 Gm. The dosage should never exceed 0.6 Gm. *It must never be injected as a simple solution*, but must be converted into the alkaline salt by adding for each 0.1 Gm. of arsphenamine, dissolved in 25 cc. of water, 0.85 cc. of exactly titrated normal NaOH solution. This should stand thirty minutes before using. It should not be shaken. Further directions accompany the packages. It is inadmissible to use the contents of damaged tubes or remnants of powder from previously opened tubes. To prevent the injection of acid arsphenamine, it is advisable to add two drops of a 1 per cent alcoholic solution of phenolphthalein, which gives a deep yellow color if the solution is properly alkaline (S. Chambers, 1928).

Sulfarsphenamine, U.S.P., Sulfarsenobenzene, 20 per cent As (the same as neoarsphenamine), is a yellow, dry powder; odorless; freely sol. in water. More stable than neoarsphenamine, but slowly oxidizes on exposure to air, becoming darker and more toxic. Dose (by intramuscular injection), usually 0.4 to 0.6 Gm. for men, 0.4 Gm. for women, dissolved in sterile, freshly distilled water in the proportion of 0.1 Gm. to 0.3 cc.; for intravenous injection, 0.1 Gm. to 2–5 cc. It is employed mainly when intravenous injection is undesirable, as in children. Its therapeutic potency is satisfactory. Though originally credited with special efficiency in neurosyphilis, it was discredited by further experience. *Untoward reactions* are about the same in kind and frequency as with neoarsphenamine; purpura hemorrhagica is more frequent with sulfarsphenamine, icterus with neoarsphenamine (T. F. Probey *et al.*, 1944). Children appear to tolerate it better than do adults. The toxicity for animals is about the same as for neoarsphenamine. *Trisodarsen*, formerly Triarsen, trisodium arsphenamine disulfonate (with some inert diluent), has been investigated chiefly by Stokes and Beerman as a substitute for neoarsphenamine. It is more stable in air than are neoarsphenamine and sulfarsphenamine. Its therapeutic potency is reported as between neo- and old arsphenamine. The frequency of reactions is about the same as with neoarsphenamine; its toxicity for animals is somewhat lower (Report, Council on Pharmacy and Chemistry, 1937, J.A.M.A., *109:* 1125). *Acetylglycarsenobenzene*, sodium diacetylaminohydroxyarsenobenzene glycolate, SS371, solusalvarsan, has been introduced as a water-soluble arsphenamine derivative suitable for intramuscular injection. It appears promising, but requires further study. It is a yellow, odorless powder, readily soluble in water, and contains 28.3 per cent of As. It appears to be less effective than neoarsphenamine

Its intramuscular injection is often painful, and arsenical toxic reactions appear to be rather common (L. W. Harrison, 1939; Report, Council on Pharmacy and Chemistry, 1940, J.A.M.A., *115:* 1635). *Silver arsphenamine,* N.N.R., is a combination of sodium arsphenamine and silver, containing 20 per cent of arsenic (the same as neoarsphenamine) and about 13 per cent of silver. Readily soluble in water. Dose, 0.25 to 0.3 Gm. for men, 0.2 Gm. for women, as 0.5 per cent solution intravenously. It may produce argyria, although rarely. It was introduced especially for neurosyphilis, with the claim that the silver enhances the potency (Kolle, 1920), but it is doubtful whether it has any special value. *Bismarsen,* N.N.R., bismuth arsphenamine sulfonate of sodium, contains about 13 per cent of arsenic, 24 per cent of bismuth. It is used intramuscularly and acts more slowly than sulfarsphenamine.

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TELLURIUM

The pharmacological actions of tellurium and selenium are rather similar to those of inorganic arsenic, especially the toxic effect on the capillaries. Tellurium is relatively nontoxic, however, being rapidly reduced to the metallic state. Its most conspicuous effects are suppression of sweat, and a persistent garlic odor, especially of the breath, due to methyl telluride. These effects are noted in the industries dealing with tellurium. Sodium tellurate has been used to suppress the night sweats of phthisis. It is somewhat spirochetocidal in rabbits (Levaditi and Nicolau, 1926).

The *relative toxicity of the salts of the metals of the arsenic group* was investigated for rats by intraperitoneal injection by K. W. Franke and Moxon, 1936. The M.F.D. mg. per Kg. to kill 75 per cent of the animals in forty-eight hours was as follows: Na_2SeO_3 = 3.25 to 3.5; Na_2SeO_4 = 5.35 to 5.75; Na_2TeO_3 = 2.25 to 2.5; Na_2TeO_4 = 20 to 30; Na_2HAsO_3 = 4.25 to 4.75; Na_2HAsO_4 = 14 to 18; $NaVO_3$ = 4 to 5; $(NH_4)_6Mo_7O_{24} > 160$. *For ingestion with food,* at levels of 25 to 50 ppm, they found the toxicity to decrease in the sequence of As>Mo>Te>V>Se.

Compounds.—The more important are tellurous oxide, TeO_2; telluric oxide, TeO_3; sodium tellurite, Na_3TeO_3, and sodium tellurate, Na_2TeO_4; hydrogen telluride, H_2Te; methyl telluride, $(CH_3)_2Te$; and tellurium tartrate, $Te(C_4H_5O_6)_4$.

Solubility.—The sodium salts are soluble in water; but the tellurite would be transformed into insoluble tellurous oxide by the acidity of the gastric juice. The alkalinity of the intestine, however, would restore the tellurite. Tellurous oxide itself would therefore be dissolved in the intestines.

Absorption from the alimentary tract is incomplete, since all the compounds are rapidly reduced to metallic tellurium, which is eliminated by the feces, imparting a blue or gray color to these. A small proportion, however, is easily absorbed, apparently even from the intact skin, for even a trace adhering to the skin imparts the garlic odor to the breath.

Reduction in Body.—All living cells rapidly reduce all tellurium compounds to the metallic state, recognized by the greenish, blue-green, blue, or dark gray-blue color, according to the quantity (Kunkel). After intravenous injection, this is found in all the organs, particularly abundant in the liver and kidneys; the lungs, spleen and adrenals are relatively free. Hofmeister, 1894, pointed out that the distribution of this reduction is quite different from that of dyes. The reduced metal is in an ultramicroscopic state. Beyer claimed that it is in the cell nuclei. The deposition of the reduced metal throughout the body occurs also with oral administration. It remains in the cells for a long time, but part is continuously transformed into methyl telluride. This explains the persistence of the odor.

Reduction by Micro-Organisms.—Gonis, 1905, showed that living bacteria and other micro-organisms reduce tellurite (also selenite). As dead organisms do not effect this reduction, potassium tellurite may be used as an *indicator of living bacteria,* yeasts, molds, and so forth. When incubated for twenty-four hours with a concentration about 1:50,000, living cultures of all the more common micro-organisms reduce the tellurite, as indicated by the appearance of a black precipitate. This concentration is practically harmless when injected into animals (W. E. King and Davis, 1914).

Excretion.—With oral administration, the major part is reduced to the metallic state, and is excreted as such unabsorbed by the feces. That which is absorbed is excreted partly as methyl telluride by the breath, urine and feces, and partly as a soluble form in the urine and bile (Mead and Gies, 1901).

Methyl Telluride.—A pronounced odor of garlic, due to methyl telluride $(CH_3)_2Te$, appears in the breath within five minutes after administration by any channel and in all animals. It persists for several days up to eight months after a single dose, according to the quantity taken. In man, it has been noted after as little as 0.0005 mg. (Reisert). The odor was described by Gmelin, 1824, and by Hansen, 1853, who made the first pharmacologic investigations of tellurium. The odor is also present, though less marked, in the urine, feces, epidermal excretions, blood and viscera. Hofmeister found that methyl telluride is produced by all tissues; also when tellurite is digested with finely mashed organs *in vitro;* but that it is prevented by any agents that tend to disorganize protoplasm, even by water or normal saline. Saponin has little effect, and quinine restrains only in fairly high concentrations. There is no parallelism between the formation of methyl telluride and the reduction to metallic tellurium. Methyl telluride is also produced by cold-blooded animals and invertebrates (earthworms), not by the higher plants (Knop, Bokorny; quoted from Gies and Mead). "*Bismuth breath*" has been attributed to contamination of bismuth preparations with tellurium; the two substances often occur in association.

The *toxicity* is low for oral administration, higher for hypodermic injection. The tellurite is perhaps ten times more toxic than the tellurate. Commercial tellurate, however, often contains tellurite. Colloidal tellurium is also much less toxic. Martelli, 1914, claimed that the toxicity to rabbits is greatly increased by coccidiosis of the liver. Berzelius found hydrogen telluride and selenide more irritant and toxic than hydrogen sulfide. The toxic and fatal doses may be found in the papers of Mead and Gies; Brutti; Martelli; Czapek and Weil; and de Angelis.

Metallic Tellurium.—Hofmeister showed that this is gradually converted into the active form in the tissues, for the garlic odor occurred after intravenous injection of the finely powdered metal.

Colloidal tellurium was investigated by de Angelis. He found it much less toxic than the tellurite. Indeed, the effects were not proportional to the dose. He attributed this to limited power of the organism to transform it into hydrogen telluride, which he assumed to be the really active agent.

Acute Toxic Phenomena in Mammals.—The essential features were described by the earliest investigators, Gmelin, 1824, and Hansen, 1853. Czapek and Weil, 1893, made a comprehensive study and pointed out the close resemblance to selenium and arsenic; the effects of tellurium, however, are slower and less virulent. They start with somnolence; restlessness, tremors, vomiting and diarrhea; asphyxial convulsions and death. The muscles and nerves remain irritable to the end. The *pathological lesions* are: severe gastro-enteritis, intense hyperemia of viscera and lungs, hemorrhage from mucosae, fluid in the serosae, parenchymatous nephritis (Martelli, 1914).

Symptoms in Man.—The inhalation of tellurous oxide in fairly large quantity results in nausea, metallic taste, the garlic odor, somnolence, depression and constipation (Mead and Gies). The same symptoms are described for hydrogen telluride. Hansen took a total of 0.34 Gm. of potassium tellurate, distributed over a long period. He recorded unusual sleepiness, nausea, anorexia and abundant salivation.

Toxic effects on frogs are interpreted by Czapek and Weil mainly as paralysis of the central nervous system. Skeletal muscle shows fibrillary twitching, even at a distance from the site of injection. With tellurite, there is also a curare action (Labes, 1929). The heart becomes paralyzed late in the poisoning.

Effects on Circulation.—Czapek and Weil observed characteristic arsenic effects, attributed to paralysis of the capillaries: profound fall of blood pressure and dilatation of splanchnic vessels, with good pressure response of the heart and vasomotor system. The *cardiac vagus* remains excitable late in the poisoning.

Digestive Tract.—Czapek and Weil found that dogs and cats respond to large doses by vomiting and diarrhea, the stools becoming of a rice-water and finally mucous character. The necropsy shows the mucosa of the duodenum and jejunum congested, swollen, with small hemorrhages, covered with a pseudomembrane; the epithelium is desquamated. The ileum and colon are usually quite normal. Rabbits generally die without gastro-intestinal symptoms. Subemetic doses do not interfere with digestion. Even fairly high concentrations do not affect gastric and pancreatic digestion *in vitro*. Ptyalin is perhaps somewhat checked (Mead and Gies).

Blood-Forming Organs.—The changes in these are analogous to those from arsenic. Martelli studied especially the bone marrow in rabbits and guinea pigs. With *small doses*, there is hyperplasia. *Moderate doses* cause leukopenia and hypoplasia. The animals tend to put on fat and increase in weight. With *fatal doses*, the bone marrow appears red, with hyperplasia of the white and red cells. If the animal survives, the picture is as for moderate doses. The *blood picture* also corresponds with that with arsenic. Small doses produce some leukocytosis, with diminution of hemoglobin. Moderate doses cause leukopenia. With rapidly fatal doses, the whites increase; the reds decrease, their resistance is lowered, and some hemolysis occurs spontaneously (de Angelis).

Hemolysis.—Luzzato found that sodium tellurite is also hemolytic *in vitro*. He believed that the action is not due to the tellurite as such, nor to the metallic tellurium to which it is reduced, but to an intermediate product, perhaps H_2Te. In confirmation, Brutti found that colloidal Te is not hemolytic *in vitro*.

Sweat.—Neusser, 1890, apparently first observed that sodium tellurate, 20 to 60 mg. per day, suppresses the night sweats of phthisis patients. The observations were confirmed by others, and this application was endorsed especially by Combemale, 1891. These doses produced no notable bad effect, except slight dyspepsia and the marked garlic odor. The latter was probably mainly responsible for the abandonment of the tellurates, for but little has been written about them since that time. Dryness of the skin and skin eruptions were noted by Shie among industrial workers. Czapek and Weil found in kittens that subtoxic doses suppress spontaneous sweating of the paws and weaken or abolish response to sciatic stimulation. Pilocarpine provokes a feeble secretion. The gland cells do not show anatomic changes They claimed that arsenic had a similar effect, selenium not.

Other Secretions.—The statements as to *saliva* are contradictory. The workers of Shie's series complained of dry mouth. Hansen recorded abundant salivation. Only little work has been done on animals; none on the saliva or mucus; little on other parasympathetic innervation. Mead and Gies reported mucus secretion markedly increased in the stomach and intestines. They found the quantity and acidity of *gastric juice* markedly diminished in dogs, even by small doses. The vomitus was never acid. *Bile* was frequently regurgitated into the stomach.

Kidneys.—Czapek and Weil often observed casts, leukocytes and sometimes red cells in the urine. Mead and Gies also record albumin after hypodermic or toxic oral doses. De Angelis, on the other hand, claims absence of albumin, unless the urine contained hemoglobin.

Metabolism.—Mead and Gies fed subtoxic doses of various Te compounds to dogs, for a week, without notable effects. The *urine* became dark colored from the reduced tellurium. Brutti, 1910, found that 30 to 50 mg. of sodium tellurate per Kg. of rabbit or guinea pig produced in about half the animals severe *glycosuria* (3 to 10 per cent of sugar), with decrease of blood sugar. Mead and Gies did not find any glycosuria after toxic oral doses. Intravenous injection of 25 to 50 mg. of colloidal tellurium into rabbits produced marked increase of *urobilin* in the blood and urine, which de Angelis attributed to the hemolysis.

Autolysis.—Fasium found that salts of Te and Se activate ordinary autolysis, while they hinder the autolysis of mouse sarcoma.

Industrial Tellurium Poisoning.—Tellurium occurs as an impurity of lead and copper ores and is encountered industrially in the purification of these metals, especially in the electrolytic refining of lead. Here it occurs in the fumes as hydrogen telluride, and in dust as tellurous oxide and tellurates. The direct industrial use is not extensive. It is employed in the glass industry, to impart a blue, red or brown color to glass. It is being tried in steel making as a reducing agent in place of coke. It vaporizes when added to melted iron in foundry practice (H. Steinberg *et al.*, 1942). Shie, 1920, and Deeds examined twelve lead workers exposed to tellurium. Eight of these showed *symptoms* that might be attributable to tellurium, and these were of about the same frequency and degree with those who had been exposed only two weeks, as with those who had worked for a year. The frequency of the symptoms among these eight affected workers was as follows: seven—garlic odor, metallic taste, dry mouth; six—dry, itching skin and rashes; five—suppression of sweat; four—constipation; three—poor appetite, nausea, vomiting, somnolence; one—loss of hair. None showed albuminuria or malnutrition.

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SELENIUM

This element is closely related to tellurium chemically and in some of its actions, but is much more toxic. Chronic poisoning produces unique effects that were overlooked in the earlier investigations, as those of Czapek and Weil, 1893, and Woodruff and Gies, 1901. These were concerned chiefly with the acute effects of relatively large doses, which seemed to have only a moderate theoretical interest. Selenium had some notoriety as a possible specific treatment of cancer, but this proved a disappointment. Relatively recently it was recognized that "alkali disease," a peculiar stock disease prevalent in certain regions of the North Central Great Plains, in Wyoming and South Dakota, is due to the ingestion of selenium in the forage and cereals grown on the volcanic soils of these regions, which are relatively rich in selenium (review, A. L. Moxon and Rhian, 1943).

Historical.—Marco Polo (1254–1327), in his account of travels in Western China, in the thirteenth century, recognized this peculiar form of stock poisoning and assigned it correctly to the forage, "a poisonous plant growing there, which if eaten . . . has the effect of causing the hoofs of the animal to drop off. Those of the country, however, being aware of its dangerous quality, take care to avoid it." The connection of selenium and alkali disease was shown by the chemists of the U.S. Department of Agriculture. The toxicology and pharmacology have been extensively investigated by M. I. Smith and his associates of the National Institute of Health.

Toxic Selenium Soils.—Selenium is widely distributed in the soil of arid and semi-arid regions throughout the world (K. T. Williams and Byers, 1934) and passes into the plants grown upon them. Soils containing more than 0.5 parts per million or vegetation with more than 5 ppm are potentially dangerous to live stock (H. G. Byers, 1935). The actual danger depends somewhat on the form in which the selenium is present, and on climatic and other conditions (H. G. Knight, 1935, 1937). It was reported that the passage of selenium into the plants could be materially reduced by treatment with sulfur or calcium sulfate (Trelease and Trelease, 1938), but this does not seem to have worked out well. The raising of cereals has been abandoned in regions where selenium abounds.

Insecticidal Contamination.—Citrus orchards in which selenium sprays had been used for five years contained a maximum of 2 ppm in the upper six inches of soil (W. M. Hoskins *et al.*, 1938), a quantity that does not appear negligible. Selenium applied directly to soils destroys red spiders and some other insects on plants, but some insects are not susceptible (review, A. L. Moxon and Rhian, 1943).

Occurrence in Vegetation.—Plants grown on selenium-containing soils take up considerable of the element. Its connection with the disease was first suspected from its isolation by W. O. Robinson from South Dakota wheat which had proved toxic to animals. It is the only mineral element known to be absorbed from the soil by food plants in sufficient quantity to render them lethal to animals. It accumulates much more in some plant species than in others, and in a few varieties, such as Astragalus, it appears to be essential to growth, so that the occurrence of these plants indicates its presence in the soil (Trelease and Trelease, 1938). In commercially purchased wheat grain from various parts of the world, its concentration ranged from 0.1 to 1.9 mg. per Kg. In that grown in soils of the selenium region it may be as high as 26 mg. per Kg. It is mostly in the gluten, and gluten from wheat grown on artificially selenized soil may contain up to 340 mg. per Kg. (W. O. Robinson, 1936). Crystallizable selenium-containing amino acids, similar to cystine, have been isolated from seleniferous grain (Horn and Jones). The concentration in most vegetables from selenium regions is rather low, except with onions, cabbage and rutabaga; in onions it may run up to 17.8 mg. per Kg. Its concentration in meat is up to 8.0 mg., in eggs to 9.14 mg., in milk to 1.28 mg. per Kg. These are the chief sources of income for man. Water is rather low, not above 0.33 mg. per liter. The bread used in selenium regions contained only up to 0.1 mg. per Kg., as it is made from imported flour. The locally grown wheat averaged 18.8 mg. per Kg., maize 14.9 mg. The seleniphile plants, such as Astragalus, may contain 150 mg. per Kg., a half more than the soil. About half of the latter is water soluble, while none of that in wheat is extracted by water.

Fate.—Extensive studies of M. I. Smith, Westfall and Stohlman, 1937, with hypodermic and oral administration of sodium selenite to animals, acutely, and continuously for two weeks to half a year, show that 30 to 90 per cent, usually 50 to 75 per cent, is excreted chiefly by the urine (although the concentration in the feces may be higher). A smaller amount is exhaled as methyl selenide $(CH_3)_2Se$. With hypodermic injection of sodium selenate (radioactive isotope) into rats, 3 to 10 per cent is excreted through the respiration within twenty-four hours (K. P. McConnell, 1942); with sodium selenite the respiratory excretion reaches 17 to 52 per cent (J. Schultz and Lewis, 1940). The urinary concentration runs closely parallel to the intake. Selenium organically bound in plants gives a considerably higher retention (about five times), as would be expected from its slower absorption. When the administration of selenite is discontinued, the excretion falls as a parabolic curve, becoming practically horizontal in about two weeks. With organic selenium the descent is slower and the horizontal higher. The quantitative determination of selenium in tissues and feces is described by R. Gortner and Lewis, 1939.

The *selenium content of the urines* in selenium regions was studied by M. I. Smith, Franke and Westfall, 1936, and M. I. Smith, 1941. Of the rural population, 92 per cent showed selenium above 0.002 mg. per 100 cc.; 73 per cent ran below 0.05 mg.; the others to 0.133 mg. The urinary concentration in animals with selenium symptoms ranges from 0.06 to 0.3 mg. per 100 cc., which would correspond to a daily intake of about 0.1 mg. per Kg. of body weight. They incline to consider concentrations above 0.02 mg. per 100 cc. as indicative of potential damage. Random urine samples of persons not exposed to selenium contained 0.001 to 0.016 mg. per 100 cc., 0.02 to 0.1 mg. per day (J. H. Sterner and Lidfeldt, 1941).

Organ Distribution.—Selenium administered as inorganic or organic compounds is distributed through all the tissues with special predilection for the liver and kidneys, and in descending order: pancreas, spleen, heart, lungs, brain. Hair contains considerable selenium in chronic poisoning and is perhaps an index of the amount of exposure. The blood concentration is usually low, the corpuscles much higher than the plasma. It passes into the fetus (H. C. Dudley, 1936; Gortner and Lewis, 1939; M. I. Smith, 1941). After discontinuing the exposure of sheep, the organ content falls to a harmless level in about two months (I. Rosenfeld and Beath, 1945).

Phenomena of Selenium Stock Poisoning ("Alkali Disease").—The chronic form ordinarily seen causes emaciation, stunted growth, stiff gait, loss of hair, especially of the tail and mane, and a peculiar deforming atrophy of the hoofs, leading to transverse ridging, erosion and separation at the coronary band. There is also a peculiar hepatic change. Reproduction is impaired. The disease is especially injurious to young animals. The hoof condition may occur in the fetus, which may be born without hoofs. Horses imported into a virulent selenium region develop the condition in about three months. It is exacerbated in spring and autumn. More intensive poisoning leads to incoordination, "loco" or "blind staggers," but it is questionable whether selenium is responsible for all cases of these ill defined conditions. Acutely fatal poisoning may ensue from liberal consumption of plants with especially high selenium content, but these are not eaten by the animals unless forced by hunger—probably not by an antiselenium instinct, but because they happen to have a strong odor or taste. *Chickens* are peculiarly resistant to selenium poisoning, but their *eggs* develop only partly and do not hatch, and the embryos are greatly deformed. The production of eggs is not materially decreased. Turkey eggs show the same changes. This effect occurs when the soil contains 1 ppm of selenium, or even less, and is a delicate index that a farm is selenium tainted. It is diminished by adding arsenic, 5 to 10 ppm, to the feed (B. Ivory, 1945). Small quantities of selenium injected into normal eggs lead to deformed embryos (K. W. Franke, Moxon *et al.*, 1936). *Goldfish* kept in water containing sodium selenite equivalent to 2 ppm develop anorexia and die in eighteen to forty-six days (M. M. Ellis *et al.*, 1937).

Chronic selenium poisoning in the human inhabitants of selenium districts is unlikely, as their food does not come exclusively from the region. However, the urinary output of about a fourth of the inhabitants is about a third of that of animals with selenium disease, so that the margin is not wide. Smith, Franke and Westfall, 1936, found no serious illnesses attributable to selenium, and not a conspicuously high incidence of minor gastric, hepatic, neuritic, finger-nail, dental or other disturbances that might be attributable to selenium, but which are not characteristic.

Industrial chronic selenium poisoning is a potential hazard, as selenium is given off in lead, zinc and copper smelters and is widely used in ceramics, paints, steel, copper alloys and rubber manufacture. The domestic consumption in 1935 was 412,000 pounds, four times that of 1921. The urine of workers in a copper refinery contained from traces to 0.69 mg. per 100 cc. (the maximum being over twice that in selenium stock poisoning). Gastro-intestinal disturbances, nervousness, pallor and garlic odor were observed. The selenium content of the air and of the urine of the workers should be watched (H. C. Dudley, 1926, 1938). Acute sore throat was observed by Motley *et al.*, 1937, in *laboratory workers* handling animals treated with selenium compounds (possibly exhalation of methyl selenide). The dogs showed marked edema of the lungs and concentration of the blood.

Typical chronic selenium poisoning is produced experimentally in rats and guinea pigs by feeding grain grown on artificially selenized soil (H. C. Knight, 1934). Severe toxic effects occur with 15 mg. per Kg. of food, corresponding to a daily intake of 1 to 1.5 mg. per Kg. of body weight. Organic selenide is about half as toxic as the selenium in grain (O. G. Fitzhugh *et al.*, 1944). The phenomena have been studied with sodium selenite especially on rats. These are peculiarly resistant to the acutely fatal action so that it is possible to continue relatively large doses which produce cumulative pathological lesions; but if the rats are given a choice of foods they avoid the selenium. At the threshold dosage of 0.1 mg. per Kg. of body weight per day (corresponding to about 0.1 to 0.5 mg. per 100 cc. of urine), these lesions include injury to the gastric mucosa, focal destruction and fatty necrosis of liver cells, anemia and focal cardiac degeneration, with symptoms of anorexia, vomiting and lowered liver function. They progress to gastric ulcers; severe necrosis and degeneration of the hepatic parenchyma, with periportal cirrhosis; similar but less severe renal changes; preliminary anhydremia followed by progressively severe hyperchromic anemia; hyperplasia of the reticulo-endothelial system; serous effusions; epiphyseal erosions of the bones; cachexia and malnutrition, diminished fertility (K. W. Franke and Potter, 1936; M. I. Smith, 1941). J. Seifter, Ehrich *et al.*, 1946, describe the production of thyroid hyperplasia and adenomatous liver by an organic selenium compound. The unique hepatic cirrhosis occurs in about 70 per cent of the rats that have been on selenium diet for three months (O. G. Fitzhugh *et al.*, 1944). It may be followed by adenoma or low grade carcinoma (A. A. Nelson *et al.*, 1943). It is preventable by the administration of sodium arsenite and arsenate; tungstate is less effective; other elements, including molybdenum and vanadium, are ineffective or increase the damage (Moxon and DuBois, 1939; K. P. DuBois *et al.*, 1940). Sodium arsenite also decreases the general toxicity of selenium. The detoxication applies to all forms of selenium and is not due to interference with intestinal absorption, for it is independent of the route by which either the selenium or the arsenic is administered (A. L. Moxon *et al.*, 1945). Various proteins in food protect against chronic selenium poisoning. This is not related to their cystine or methionine content (Smith and Stohlman, 1940). Rats with symptoms of selenium or tellurium poisoning show marked decrease of the *ascorbic acid* content of the liver and adrenals (Svirbely, 1938). Similar chronic poisoning is observable in *dogs* when 7.2 ppm of natural organic selenium, or 10 ppm of sodium selenite, are added to the diet; with similar protection by arsenic (M Rhian and Moxon, 1943).

The *acute toxicity* of selenium compounds is high. For dogs, 4 mg. of sodium selenite or selenate per Kg. of body weight, by oral, hypodermic or rectal administration, are usually fatal in a few minutes. The powdered metal is much less toxic by mouth. Even 4 Gm. per dog are nontoxic, being mainly excreted by the feces (Czapek and Weil, 1893). For cats, rabbits and rats, the M.F.D. ranges from between 1.5 and 3 mg. per Kg., the selenite and selenate usually alike, and oral about half as toxic as intravenous (Smith, Stohlman and Lillie, 1937). *Selenium oxychloride*, $SeOCl_2$, is highly vesicant, producing painful, slow-healing burns. Rabbits die within twenty-four hours after the application of 0.01 cc. to the skin, with Se demonstrable in the liver and blood (H. C. Dudley, 1938). Organic selenium compounds are much less toxic (Moxon *et al.*, 1938). The toxicity of *selenium cystine* was studied by A. L. Moxon, DuBois and Potter, 1941.

Embryos.—A small amount of a selenium salt injected into the air sac of hens' eggs, after incubation, gives rise to monstrosities similar to those that form in the eggs of hens fed on selenium grain. Arsenic, fluoride and lead do not produce monsters (K. W. Franke *et al.*, 1936).

A specific effect on cancer in rats was claimed for intravenous injection of selenium compounds by Wassermann, Keysser and Wassermann, 1911, 1912, but it proved unreliable (Keysser, 1914). Czapek and Weil found sodium selenite practically nontoxic for *protozoa* or *ciliated cells.* It checked alcoholic and bacterial *fermentations*, being reduced to the red metallic selenium. The *oxygen uptake* of living yeast cells is markedly inhibited by low concentrations of sodium selenite (V. R. Potter and Elvehjem, 1936). The *metabolism of tissue slices* of rats' liver, brain and kidneys (but not of muscle) is decreased by dilute solutions of sodium selenite (H. A. Schneider, 1936) and by diseleno-diacetic acid (C. I. Wright, 1939). Sodium selenite inhibits oxygen consumption by tissues *in vitro,* apparently by poisoning succinic dehydrogenase (M. E. Collett, 1924), not on the cytochrome oxidase component (E. A. Stotz and Hastings, 1937). It, and selenate, inhibit urease at *p*H 5, but not arginase of rat's liver, *in vitro* (C. I. Wright, 1940). The inhibition of urease is probably through oxidation of its sulfhydryl group, and the removal of this group is perhaps involved in the general toxicity (Smith, 1941; E. P. Painter, 1941).

Hemoglobin.—Hydrogen selenide acting on ferri-hemoglobin solutions produce a compound analogous to hydrogen sulfide hemoglobin (R. D. Barnard and Neitzel, 1938).

Higher Plants.—The presence of selenium in soils is deleterious to most plants, including cereals, decreasing their growth rate, and higher concentrations cause extreme chlorosis and death. *Tellurium* is similarly toxic (A. L. Martin, 1936, 1937; Hurd-Karrer, 1937). The addition of a sulfate to the soil reduces the selenium content of plants and thereby renders it less toxic. Certain species of Astragalus (not all) and a few other "indicator" plants take up selenium selectively and are stimulated to increased growth by concentrations that kill wheat or buckwheat (S. F. Trelease, 1940).

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VANADIUM

Chronic vanadium poisoning occurs clinically in workers exposed to it, in its production, through its industrial use as a mordant and by the wearing of dyed fabrics. The symptoms are those common to other chronic metal intoxications (Dutton, 1911). The lungs, kidneys and digestive canal are especially affected. Dust and fumes cause irritation of the exposed mucosae, bronchitis with a characteristic dry paroxysmal cough, sometimes so severe as to cause hemorrhage; emaciation; increased susceptibility to tuberculosis. Anemia and a peculiar cachexia are early symptoms. Digestive derangements, vertigo, hysteria, melancholia may develop; also fine tremors of the hands and failure of sight. Hemorrhagic nephritis has been reported. *Experimental chronic poisoning* in animals shows similar symptoms (Ballotta, 1931; E. P. Daniel and Lillie, 1938. Symanski, 1939, claims that industrial exposure, chiefly to the dust of the pentoxide, V_2O_5, causes only local irritation of the exposed mucosae, and no systemic effects).

The *distribution* of vanadium in biological material is reported by E. P. Daniel and Hewston, 1942. When sodium tetravanadate was injected intravenously into man, 81 per cent was *excreted* in the urine in seven days, and 9 per cent in the feces (N. L. Kent and McCance, 1941).

The **acute symptoms** produced in rats by oral administrations of sodium meta- or orthovanadate are similar to those of chronic poisoning: immediate intense distress, hemorrhage from the nose and intestines, marked diarrhea, often paralysis of the hind legs, dyspnea, convulsions. Postmortem examination shows acute desquamative enteritis. Continued administration of tolerated doses does not produce cumulation (E. P. Daniel and Lillie, 1938).

Circulatory Effects.—With intravenous injection of sodium orthovanadate, D. E. Jackson, 1912, found rise of blood pressure due to systemic vasoconstriction, by direct action on the arterial muscle or vasomotor endings. The heart is not strengthened. The pressure in the pulmonary artery also rises by the systemic and pulmonary vasoconstriction. Perfused lung vessels are strongly constricted (Baehr and Pick, 1913). *Bronchial muscle* also shows moderate but prolonged constriction (confirmed by Baehr and Pick, 1913).

Vanadium chloride and bromide (VCl_3 or VBr_3), investigated by Luzzato, 1903, cause the usual anatomic lesions of metals in the kidneys, liver, intestines and stomach. No lesions are found in the central nervous system. The blood pressure is raised and the excitability of the vagus is depressed. Death occurs through respiratory paralysis.

Spirocheticidal action has been reported for rabbits (Levaditi *et al.*, 1928), and clinically by Pereira, 1939 The latter injects vanadium sodium tartrate, 0.15 Gm. in 2 cc. of water, intramuscularly, twice a week. He reports prompt disappearance of the spirochetes and secondary lesions, and of gummas that had been refractory to bismuth and arsphenamine. It is also effective in frambesia. The toxicity is low; stomatitis, erythema and hepatic disorders are rare sequels.

Therapeutic Use.—The pharmacologic actions do not point to any definite therapeutic usefulness. Vanadium has been tried as an alterative similar to arsenic, in tuberculosis, diabetes, and so forth, but the results are not convincing. It was administered as *sodium metavanadate*, a white, almost tasteless powder, sol. in water. Dose, 1 to 8 mg. ($\frac{1}{60}$ to $\frac{1}{8}$ grain).

TUNGSTEN

The toxicity for rats on oral ingestion is reported by F. W. Kinard and van de Erve, 1941; the effects and excretion after hypodermic injection by Selle, 1942; its organ distribution by F. W. Kinard and Aull, 1945.

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TITANIUM

Titanium dioxide, TiO_2, is applied to the skin as ointment or wash to protect against sunburn. It produces no local irritation or systemic effects (Ballotta, 1931). The oxide or orthotitanic acid can be administered to rabbits by stomach tube in considerable doses for several weeks. They are absorbed without apparent effects. M. C. L. Bernheim, 1940, reported changes in the sulfur metabolism, *in vitro*, and with intraperitoneal injection, probably by inhibition of the oxidative enzymes. The *distribution* of titanium in man was reported by Maillard and Ettori, 1936.

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MOLYBDENUM

Molybdenum occurs normally in the tissues of all animals examined; in vertebrates it averages 2 mg. per Kg. of dry weight; in invertebrates, 0.8 mg. (D. Bertrand, 1942). It is not very toxic even when inhaled as dust or fumes in industry (review, L. T. Fairhall, 1945). The pharmacological effects of molybdenates were studied by Agnoli, 1933.

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URANIUM

The salts are corrosive, readily absorbed, and highly toxic. They injure the capillaries and cause a characteristic nephritis, both tubular and glomerular; hepatitis; glycosuria and acidosis and a unique edema. The renal and hepatic epithelium regenerates readily. Acute poisoning stimulates and then paralyzes the respiration, resembling cyanide. Animals survive the lethal dose of uranium nitrate if a liberal amount of sodium citrate is injected by vein, even three days later (G. L. Donnelly *et al.*, 1944).

Oral Intoxication by Insoluble Uranium Compounds.—Although uranium oxide and uranyl nitrate are nearly insoluble in water, they are highly toxic when given by mouth (to guinea pigs), since they are fairly soluble in dilute hydrochloric acid (Karsner *et al.*, 1918). Hypodermic injection of colloidal uranium is less toxic than nitrate (Maloney and Burton, 1938).

Influence of Light.—The resistance of guinea pigs to uranium poisoning is decreased if they are kept in the dark, but this is reversed by the injection of eosin (Karsner, Shen and Wahl, 1922).

The **excretion of uranium** occurs mainly by the kidneys (Karsner, Reimann and Brooks, 1918); none in the bile.

Distribution.—Retained uranium is deposited chiefly in the renal cortex. About a fifth (1 to 50 per cent) is contained in the liver. Very little is found in the other organs (Eitel, 1928; H. D. Jones and Goslin, 1933).

The **acute effects** were studied, especially by Woroschilsky, 1890, and D. E. Jackson, 1910. The respiration is first increased, then paralyzed. This results in asphyxial phenomena, stimulation of the vasomotor center and rise of blood pressure. The respiratory paralysis is the cause of death. The blood is rendered noncoagulable by an unknown mechanism. **Sublethal doses** are followed in a few days by albuminuria and glycosuria; parenchymatous degenerations; gastro-intestinal disturbances; paralytic symptoms and changes in the blood vessels.

The **anatomic changes in uranium nephritis** affect both the tubular epithelium and the glomeruli (Fleckseder, 1907). The vascular mechanism is involved first, but the tubular changes progress longer and finally predominate. The anatomic and functional changes are more severe in old animals, and are increased by anesthetics, especially chloroform (MacNider, 1914). Sodium citrate administration confers some protection, increasing the uranium excretion up to four times (G. E. Gustafson, 1944). Dogs are more resistant than rabbits (O'Hare, 1913). The epithelium shows fatty changes; the glomeruli are congested; or the glomeruli shrink, with enlargement of the glomerular space (Tribe *et al.*, 1916). Christian *et al.*, 1911, described characteristic hyaline droplets in the vessel walls of the glomerular tufts. These do not occur in other vessels of the kidneys or in other organs. The tubular epithelium regenerates completely within two weeks, and the regenerated epithelium is much more resistant to uranium (W. C. Hunter, 1928). The nephrotoxic action also extends to the fetus (M. Bodansky *et al.*, 1933). Repeated injections of small doses produce chronic interstitial nephritis with fibrous changes, not so severe as with chromates (R. M. Smith, 1911). The histologic lesions are similar to human chronic diffuse nephritis, but not quite identical. They are not associated with arterial lesions (Dickson, 1912). Some samples of uranium produce extensive *arterial calcification* in rabbits; in the kidneys this also involves the microscopic vessels and the glomerular capsules (P. Dominguez, 1926, 1928).

Regeneration.—Liver and kidney cells injured by relatively large doses of uranium, mercury or chloroform are replaced by less differentiated but more resistant cells of embryonic type, which probably are in turn replaced by normal cells (McNider, 1919, 1942).

Urine Changes.—In the early (vascular) stages, the quantity and specific gravity of the urine are increased. Albumin, glucose and acetone substances appear especially in older dogs (MacNider, 1914). A further increase of urine flow may be secured by caffeine or salines, although the response is slower than normal (Mosenthal and Schlayer, 1913). With the appearance of the epithelial changes, the urine decreases, the tubules being obstructed by the swelling and desquamation of the cells. This is not relieved by diuretics, although the vascular response to the diuretics may be preserved (MacNider, 1915). The excretion of chlorides and urates is diminished in acute, somewhat increased in the subacute, nephritis; *i. e.*, it varies in the same direction as the urine flow. Pohl described a subacute nephritis in rabbits, with polyuria until death, and with increased excretion of nitrogen and diminished chloride output. Dünner, 1915, found this inconstant. The intravenous injection of calcium or of hypotonic NaCl converted this subacute nephritis into an acute form. Isotonic saline had no effect. In this stage, the renal vessels are engorged and the blood flow through the kidneys is increased, but the oxygen consumption is diminished (Tribe *et al.*, 1916). A similar hyperemia exists in the spleen and other organs (Brull, 1934). The excretion of endogenous *creatinine* is diminished in both stages; but injected creatinine is completely excreted in the subacute, retained in the acute (Kraus, 1913). The *phenol-s-phthalein excretion* also varies in the same direction as the urine flow (Eisenbrey, 1913). It bears no definite relation to the histologic lesions (Smith, 1911). The most marked effect of uranium nephritis is a depression of the factor: urine urea divided by plasma urea. This is fairly parallel to the anatomic injury (Watanabe *et al.*, 1917). The nonprotein *nitrogen retention* in the blood goes parallel to the phthalein retention; both increase and recover together, except that the phthalein responds more promptly (Frothingham *et al.*, 1913; Karsner and Denis, 1914). However, Mosenthal, 1914, pointed out that the increase of nonprotein nitrogen in the blood is not necessarily proof of retention, but could be explained by increased protein destruction or by inspissation of the blood through polyuria.

Hepatic degeneration was studied on dogs by MacNider, 1919, 1935. It is similar to that seen after mercury, and is parallel to the acidosis, rather than to the dose.

Uranium glycosuria develops on the first or second day. The action consists partly in increased permeability of the kidneys for sugar, for it may occur without hyperglycemia (Franck, 1913), and may even relieve hyperglycemia when this is due to decreased permeability of the kidney cells (Pollak, 1911). The sugar does not bear any definite relation to the other urinary constituents, except albumin, which goes fairly parallel (Wallace and Myers, 1914). Uranium may itself cause hyperglycemia, however, even when the kidneys are excised, so that part of its action must be extrarenal (Fleckseder, 1906). *Nephritic glycosuria* without hyperglycemia occurs with many nephritic poisons. With cantharides, it is attributed to increased permeability of the vessels; with uranium, chromium, tellurium, mercury and aloin, to lesions of the tubular epithelium (Luzzato, 1914).

Acidosis.—MacNider, 1916, found the toxicity of uranium associated with acidosis, sodium bicarbonate having a distinct saving effect. It also protects the uranium kidneys against anesthetics, so that these produce much less epithelial degeneration. These findings were confirmed by Goto, 1917. Karsner, Reimann and Brooks, 1918, also found that uranium poisoning is almost always accompanied by acidosis, and that this is more severe in older animals. The albuminuria always precedes the acidosis, so that the acidosis is not the cause of the nephritis. The acidosis is not due to retention, for it occurs even when the excretion of acid is increased. It is due to overproduction or inadequate combustion of organic acids (Brull and Roersch, 1934).

Uranium Hydrops.—Hypodermic administration of uranium salts produces general anasarca and ascites (Le Bret, 1854; Richter, 1904), a highly albuminous fluid transuding mainly into the serous cavities but even into the other tissues, and extending even to the fetus in the uterus (Bibergeil, 1905). Nephrectomy alone does not produce hydrops, so that the anuria does not furnish the explanation. On the other hand, the uranium hydrops occurs in nephrectomized animals, so that the kidneys are not concerned in its production (Fleckseder); nor do the histologic kidney lesions bear any relation to the edema (R. M. Smith, 1911). The fundamental change consists presumably in an altered permeability of the capillary walls (Richter, 1904). The injection of the blood of uranium animals into chromate animals also produces edema (Heinecke, 1905; Blanck, 1906). Edema, however, occurs only in animals which are freely supplied with water—otherwise the uranium causes anuria without hydrops (Fleckseder). Retention of salts is not connected with its production (Richter, 1905). In acute uranium poisoning, the *lymph flow* is not increased (Jackson, 1910). Uranium poisoning interferes with the restoration of the blood volume after saline infusion (Bogert, Underhill and Mendel, 1916).

Therapeutic Uses.—The soluble uranium nitrate was tried in diabetes mellitus and in phthisis in doses of 75 mg. (1 grain), largely diluted. The results do not justify the further employment of so dangerous an agent. *Uranium Nitrate*, $UO_2(NO_3)_2$. $6H_2O$, occurs as light yellow prisms of bitter, astringent taste. Freely sol. in water (1:1.2) or in alc. Dose, 0.01 Gm, $\frac{1}{6}$ grain, diluted, with caution.

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ANTIMONY

The actions of antimony resemble those of arsenic, differing chiefly by greater local irritation and more difficult absorption. When given by mouth, doses can be chosen whose only action is that of producing nausea or, if somewhat larger, vomiting. The intravenous injection of inorganic and organic antimony compounds is effective against various tropical protozoan infections. Excessive doses, intravenously or by mouth, produce toxic symptoms resembling those of acute and subacute arsenic poisoning. Application of antimony preparations to the skin results in local inflammation.

Antimony has an interesting *history*. Paracelsus in the sixteenth century used it as a panacea, and it was employed against the plague. Numerous deaths caused its formal proscription.

Applied to the skin, antimony chloride is a strong caustic. Antimony and potassium tartrate (tartar emetic), when applied over long periods, produces a pustular eruption. This is due to the decomposition of the double salt, which is but slightly irritant, by the acid secretion of the follicles into the more irritant antimonious oxide, Sb_2O_3, and other compounds. Such salves were formerly used for counterirritation, but have been abandoned as too destructive and toxic.

The **nauseant and emetic effects** are due mainly to the local action. "Tartar Emetic," the tartrate of antimony and potassium, is the compound usually employed internally. As an *emetic* (dose, 30 mg., $\frac{1}{2}$ grain), its action is rather slow and too depressing. As a *nauseant* it has the advantage that the dose required is only about one-tenth of that which produces vomiting. Its continued use, however, may become dangerous. It is employed mainly as a depressant expectorant in the first stages of acute bronchitis; often in the form of Wine of Antimony, 1 cc. = 4 mg., $\frac{1}{15}$ grain; or smaller doses (1 mg.) may be repeated every hour with precaution against excessive depression. It also enters into a number of compound expectorants, such as Compound Mixture of Opium and Glycyrrhiza, N.F. (8 cc. = 2 mg. of tartar emetic and 1 cc. of paregoric) and Compound Syrup of Squill (2 cc. = 4 mg. of tartar emetic).

The *mechanism of emetic effect* is chiefly reflex, for while emesis occurs both by gastric and venous administration, the latter requires much larger doses and the vomiting occurs much more slowly (Kleimann and Simonowitsch, 1872). Among animals, antimony is emetic for dogs and pigs, but not for horses, beef or sheep. The nauseant action and the increase of the salivary and bronchial secretion are also reflex (V. E. Henderson and Taylor, 1910). Like other irritants, antimony is said to increase *uric acid excretion* (Abl, 1913).

Toxicology.—Overdoses produce the same effects as arsenic, but vomiting is always a prominent phenomenon. Death may occur after 0.15 Gm. of tartar emetic. Long-continued small doses lead to a train of symptoms of *subacute poisoning*, analogous to those produced by arsenic in the same manner (Gaehtgens, 1876), including the metabolic changes. Even small amounts retard the growth of rats (Flury, 1927). Intravenous injection of antimony and potassium tartrate into rabbits causes leukopenia, with recovery in twenty-eight hours without secondary leukocytosis. The erythrocyte count is not affected (Lucia and Brown, 1934). In distinction to arsenic, selenium and tellurium, antimony is not converted into volatile compounds by molds (Knaffl-Lenz, 1913). *Chemic antidotes* are eggs, milk; and tannic acid (tea and the like) or, in its absence, magnesia. Potassium hexatantalate precipitates antimony compounds, even in the tissues; but it could be utilized only orally, since its hypodermic injection is too toxic (Rosenthal and Severin, 1912).

The *excretion* of various types of organic compounds has been studied polarigraphically by L. G. Goodwin and Page, 1943. Thirty to 40 per cent of their antimony is excreted in the first two hours after injection.

Industrial and Domestic Poisoning.—Antimony has rarely been recorded as giving rise to industrial poisoning, except through contamination with arsenic. However, the pentasulfides used in the rubber industry are fairly soluble in human gastric juice (Carlson, 1915). Industrial exposure to antimony oxide vapor resulted in skin eruption, itching and pustulation; sore gums, conjunctivitis and laryngitis; headache, anorexia and anemia (A. Feil, 1939). Antimony is sometimes used in the glaze of cheap granite ware. This should be prohibited by law (as it is in some European countries), since some samples yield from 3 to 14 mg. of dissolved antimony in a single cooking test (E. W. Miller, 1916).

Continued exposure of guinea pigs to inhalation of antimony trioxide produces moderate fall of leukocytes, especially granulocytes, pulmonary irritation, and fatty infiltration of the liver (C. V. Dernehl *et al.*, 1945).

Habituation.—The continued administration of antimony to mammals does not lead to tolerance, as is reported for arsenic, nor does arsenic habituation confer tolerance to antimony. This difference is explained by the observation that the absorption of antimony is not diminished (Cloetta, 1911); on the contrary, it is rather increased (Brunner, 1912; he claims some tolerance for 3-valent, but not for 5-valent). Protozoa also do not become immune so readily as with arsenic (Rowntree and Abel, 1912). Antimony immunity can be induced in infusoria and does not extend to arsenic (Neuhaus, 1910). Bacteria immunized to arsenic are also resistant to antimony (Marks, 1910).

Differences in Antimony Compounds.—The toxicity and trypanocidal potency of a series of organic antimony compounds are reported by L. G. Goodwin, 1944. As with arsenic, the 3-valent is more toxic (to ten times) than the 5-valent. The organic derivatives show similar relations, the side chains being relatively unimportant (Brunner, 1912; G. Bock, 1927). The relation of the *chemical constitution and therapeutic action* is discussed by Brahmachari, 1928. Cloetta found the *pyrostibiate* much less toxic than tartar emetic. *Urea-stibamine*, injected by vein, produces fall of blood pressure, by cardiac depression and splanchnic dilatation; with large increase of the liver and spleen volume (Chopra, 1927).

Stibine, SbH_3, antimony hydride, is a potent hemolytic agent. Dogs and cats are especially susceptible and die in a few hours (S. H. Webster, 1946).

Trimethylstibine, $(CH_3)_3Sb$, is far less toxic than ordinary antimony compounds. It produces mild inflammatory reactions on local application to the skin and mucosae. It lowers the blood pressure gradually, analogous to arsenic. Large doses paralyze the central system, but do not cause encephalopathy as do the methyls of bismuth, lead and tin. Dilute solutions depress the excised heart and smooth muscle; but have no effect on skeletal muscle or motor endings (J. Seifter, 1939).

Antimony Chemotherapy.—Intravenous injection of tartar emetic is highly effective against a number of tropical diseases due to animal parasites; especially against kala-azar, bilharziasis, filariasis, Schistosoma and other flukes, Delhi boil and granuloma inguinale; good results have been obtained in leishmaniasis, sleeping sickness and frambesia. The efficiency against spirochetal and malarial infections is low, presumably because the antimony is too rapidly excreted. A number of *organic compounds* have been introduced as less toxic and less irritant, but it is doutbful whether they are materially superior.

Urea-stibamine, ethylstibamine, N.N.R. (neostibosan) and sohistibosan are now preferred in kala-azar; stibophen, antimony, lithium thiomalate and neostibosan against schistosoma (E. C. Faust, 1946).

Antimony and bismuth, as well as arsenic, are highly toxic to *trypanosomes*, but not to all protozoa. As with arsenic, the trivalent form of antimony, in inorganic or organic combination, is much more toxic to protozoa, bacteria and yeast than is the pentavalent form (Friedberger and Joachimoglu, 1917).

At the suggestion of Cushny, various investigators (Plimmer and Thomson, 1907; Mesnil and Brimont, 1908; Camac, 1911, and others) successfully used injections of antimony sodium tartrate in experimental and human trypanosome infections. Rowntree and Abel, 1910, advocated certain organic compounds, such as sodium antimony thioglycollate. The trypanocidal activity of tartar emetic is greater in the presence of serum; this does not hold for arsenicals (Shilling and Goretti, 1914). Tartar emetic has proved inefficient against *malaria*, even in large intravenous doses (J. W. W. Stephens *et al.*, 1917). *In leprosy*, antimony appeared in some cases to improve the response to chaulmoogra treatment (W. H. Hoffmann, 1927), but its value appears doubtful.

Antimony potassium or sodium tartrate is too irritant to be administered intramuscularly. Intravenously, they are injected as 1 per cent solution in normal saline. The initial dose is 40 to 60 mg., $\frac{2}{3}$ to 1 grain. In bilharziasis, this is followed every second day with 0.12 Gm., stopping the course when a total of 2 Gm. has been injected (*i. e.*, about the fifteenth injection). Delhi boil requires from $\frac{1}{3}$ to $\frac{1}{2}$ Gm.; kala-azar, 3 Gm. As much as 0.24 Gm. have been given at one dose, and a total of 5.85 Gm. in eighty-six days (Christopherson); but the therapeutic dose is not far from the toxic, and is usually followed in a few hours by irritating cough, metallic taste, salivation and nausea, colic, sometimes diarrhea and occasionally by skin rashes. Electrocardiograms may show considerable changes, especially chronic bradycardia from toxic changes in the cardiac muscle, and this may result in auricular fibrillation (F. Mainzer and Krause, 1940). The icteric index rises progressively with repeated administrations, indicating a degree of liver injury (Faust).

There is less danger of cumulative poisoning than with arsenic, since the antimony is more rapidly excreted. After intravenous injection of 0.12 Gm. of tartar emetic, 30 per cent of the antimony is excreted by urine in forty-eight hours; of 1.7 Gm. injected in a six weeks course, 1 Gm. was recovered from the urine. No data are available for the feces. Antimonious oxide may be injected intramuscularly, $\frac{1}{2}$ per cent suspended in a mixture of equal amounts of glycerin and water.

PREPARATIONS.—***Antimony and Potassium Tartrate,** U.S.P. (Tartrated Antimony, Tartar Emetic); K(SbO)-$C_4H_4O_6$. $\frac{1}{2}$ H_2O; occurs as colorless, transparent crystals or white granular powder. Sweet, then metallic taste. Efflorescent, should be preserved in well closed containers. Slightly acid to litmus. *Incompatible* with alkalis and tannins. Sol. in water (1:12). Insol. in alc. Expectorant dose, 2 to 5 mg., $\frac{1}{30}$ to $\frac{1}{12}$ grain. An obsolete "Wine of Antimony" contained 0.4 per cent. *Antimony and Sodium Tartrate* is preferred for intravenous therapy (0.03 to 0.12 Gm., $\frac{1}{2}$ to 2 grains).

Antimony Lithium Thiomalate ("*Antithiomaline*"), intramuscularly, is reported to give good results in filariasis (H. W. Brown, 1944).

Antimony Sodium Thioglycollate, which contains about 37 per cent of antimony, is used against granuloma venereum, kala-azar and filariasis. It is reported to be less irritant than the tartrate, less depressing to the circulation, and less toxic parenterally (C. Pak and Read, 1939). It is used intramuscularly and intravenously. The average dose is 50 mg.; the watery *Injection*, U.S.P., is usually available as 50 mg. in 10 cc., and as 100 mg. in 20 cc. *Antimony Thioglycollamide*, N.N.R., containing about 30 per cent of antimony, is a similar compound, rather more stable and more toxic.

Stibamine glucoside ("neostam"), a relatively nontoxic antimony compound used against kala-azar (Napier, 1929), has also given good results against filaria in cotton rats (J. E. Culbertson and Rose, 1944).

Stibophen, N.N.R. ("*Fuadin*", "Pyrostib", Sodium-antimony III bis-catechol-2.4-disulfonate, containing 13.6 per cent of trivalent antimony, was introduced in Egypt against bilharzia. It appears to be the preferred agent against schistosomiasis flukes, and it is also used against granuloma inguinale (Williamson *et al.*, 1933), and kala-azar. It is administered intramuscularly, rarely intravenously, as the commercial 6.4 per cent solution, 1.5 cc. on the first day; 3.5 cc. on the second; 5 cc. on the third; then 0.5 cc. on alternate days for seven injections.

◆

BISMUTH

The ordinary basic bismuth salts are practically insoluble in water and very sparingly soluble in tissue fluids. They are therefore poorly absorbed, practically not at all from the skin and mucous membranes, and very little even from wounds or injections. They occur as fine powders which tend to adhere to surfaces, and are therefore used to furnish mechanical protection and to exclude irritants; externally on ulcers, burns and fistulas; on inflamed mucous membranes; by oral administration in gastro-intestinal inflammations and ulcers. They were introduced into medicine in 1785 by Odier of Geneva. Soluble preparations do not accomplish these objects. Bismuth compounds are also employed against intestinal amebae. They have been used as an opaque medium in roentgenoscopy, but barium sulfate has practically displaced them from this field. Because of the insignificant absorption of bismuth compounds from these surfaces they do not usually produce systemic effects. Except for a few special compounds, these occur only from application to extensive burns or ulcers, from prolonged sojourn in fistulas, and from intramuscular and intravenous injections. They resemble subacute or chronic poisoning from other metals, especially arsenic, mercury and lead. Conspicuous black spotting of the buccal and colonic mucosae, due to precipitation of bismuth sulfide, is characteristic. They may produce fatal nephritis. Soluble bismuth salts change readily to insoluble basic salts, and their intravenous injection may cause acute flocculation collapse. The *absorbed bismuth* checks treponema infection. It has largely displaced mercury as adjuvant to arsphenamine since it has material advantages of quicker action, greater potency and less toxicity. A variety of new preparations for intramuscular injection have been introduced, differing widely in speed of absorption and in the local effects.

Local Actions and Uses of Insoluble Basic (oxy) Bismuth Salts.—These form fine adhesive powders. The subcarbonate, subsalicylate and hydroxide (magma) are insoluble in water. The subnitrate and subgallate are somewhat hydrolyzed and therefore very slightly soluble (Bouček, 1910; Stingel, 1911). They have a healing effect on inflamed mucous surfaces and wounds, drying the secretion and forming a protective covering or scab. This action is partly mechanical (H. H. Meyer, 1885), and other indifferent powders have a similar effect. A small amount of bismuth goes into solution, however, and is astringent and mildly antiseptic. The insoluble bismuth compounds are *applied* as dusting powder or ointment (30 per cent) in inflammations of the skin; and to small ulcers and burns, but in these the dry powder tends to form hard crusts which prevent effective cleaning. The application to large surfaces may result in poisoning (T. Kocher, 1882). With mucous membranes, the catarrhal mucus may prevent effective contact. Suspensions containing 10 per cent of bismuth subnitrate may be injected in urethritis. The injection of *Beck's bismuth-petrolatum paste* (1:2) into chronic abscesses and suppurating sinuses is often effective, but bismuth and nitrite poisoning may occur. The technic and precautions are described by E. G. Beck, 1916. There is little difference between the actions of the *subcarbonate and subnitrate;* on the whole, the subcarbonate deserves the preference, since it cannot give rise to nitrites. Although the subnitrate consists of sharp-pointed microscopic crystals, it does not cause mechanical irritation even when dusted on the conjunctiva.

The *soluble bismuth salts* lack the soothing qualities which constitute the main value of the insoluble products. The double citrates are indeed partly precipitated in the acidity of the stomach; but the quantity of the precipitate is too small to be effective. Various *organic salts* have been introduced as substitutes, such as subgallate (Dermatol), especially for dusting powders, but it is questionable whether they are superior to the more economical older products.

Use in Digestive Disorders.—The basic bismuth salts form a protective coating over the mucous surface of the gastro-intestinal tract. The subcarbonate (not the subnitrate) is a slowly acting antacid. They bind hydrogen sulfide (Stingel, 1911), so that the stools are black; they are among the most effective of the nonirritant intestinal antiseptics (Sollmann, 1908). These actions render bismuth subnitrate, or preferably the subcarbonate (0.5 to 2 Gm., 8 to 30 grains, every two or four hours), useful for allaying *diarrhea* (x-ray observations, Hesse, 1913) and *gastritis* and sometimes against vomiting. The bismuth powders are similarly useful in *gastric ulcer* (1 to 2 Gm. suspended in fluid, before each meal), diminishing gastric secretion and acidity (Bastedo). In *intestinal amebiasis,* bismuth subcarbonate is an adjuvant to the more active amebicides (Anderson and Reed, 1934). In normal individuals, bismuth is only moderately *constipating* since the action is on the inflammation, and not directly on the peristalsis. The continued use of these large doses may become detrimental by covering the intestinal mucosa with bismuth concretions. A small amount of the basic bismuth salts is dissolved by the acid gastric juice, is *absorbed,* and excreted by the urine (Dorner and Weingaertner, 1909), mouth and large intestines. The quantity is not sufficient to produce systemic effects.

The *use of bismuth in gastro-enterological roentgen diagnosis* is obsolete. About 50 Gm. (2 ounces) of bismuth subcarbonate (not the subnitrate) were administered, suspended in buttermilk or thick soup. Best and Cohnheim, 1911, found that the bismuth meal delays the emptying of the stomach by an hour.

Nitrite Poisoning.—The use of the relatively enormous doses of bismuth subnitrate for radiodiagnostic purposes caused several intoxications, with methemoglobinemia, intense cyanosis, diarrhea, dyspnea and death by arrest of respiration. These effects are not due to the bismuth, but to the production of nitrite by the reducing action of putrefactive fecal bacteria, especially in the large intestines and rectum (Zadek, 1914). Methemoglobin poisoning with recovery has been reported from a total of 12 Gm. prescribed against digestive disorders (G. E. Miller, 1945). E. J. Stieglitz, 1930, suggested *therapeutic utilization* of this continuous nitrite formation against arterial hypertension, administering bismuth subnitrate, 10 grains, three times daily, but carefully controlled cases failed to show benefit, even with prolonged use of fairly large doses (Ayman, 1932).

Effects on Syphilis.—Bismuth, when absorbed in small, nontoxic quantities from the intramuscular injections of its compounds, checks and suppresses treponemal infections. It was first used against the spirochetosis of fowl, by Robert and Sauton, 1916; its efficiency against syphilis was demonstrated on rabbits by Sazerac and Levaditi, 1921; and on man by Fournier and Guenot, 1921. M. F. Balzer of Paris narrowly missed making the discovery in 1889. He had actually planned to try bismuth against syphilis, but abandoned the idea because of toxic effects on dogs.

In the clinical use of bismuth by intramuscular injection, the treponemas disappear from the primary lesion in three or four days and the chancre undergoes rapid cicatrization; the contagious syphilides heal almost as rapidly as under arsphenamine; the cutaneous and visceral lesions, gummata and bone changes begin to recede after three or four injections; the response of the neurosyphilitic phenomena is about as with arsphenamine and better than with mercury; the serologic reactions respond more slowly and less frequently than with arsphenamine, especially in the primary stage where the Wassermann reaction remains positive in about a tenth of the patients under arsphenamine and in a sixth under bismuth. In the secondary stage, the difference is less marked (arsphenamine 1:6, bismuth 1:4.3; Lèri, Tzank and Pèron); but half the cases in which the Wassermann reaction resists arsphenamine and mercury become negative under bismuth. Others have estimated the relative antisyphilitic efficiency of bismuth as seven to eight-tenths that of arsphenamine, and that of mercury as four to six-tenths. The promptness and degree of the antisyphilitic action of bismuth are intermediate between that of arsphenamine and mercury, somewhat nearer to the former; and it may be substituted for either of these, especially with patients in whom these drugs are contraindicated or not tolerated, and in whom they have failed. The action of bismuth on spirochetes is probably closely analogous to that of arsphenamine, since the combined potency of both drugs in rabbit syphilis is not potentiated; it is, however, fully additive, while the toxic action is less than additive, so that the margin of safety is increased (N. M. Clausen *et al.*, 1942). Syphilis may be treated by bismuth alone, but this is not advisable; alternation of at least two agents is preferable, and one of those should be an arsphenamine. Bismuth is inferior to arsphenamine in fresh infections, and increases in value in the second stage. It has displaced mercury almost completely chiefly because it is not so likely to become injurious. Infants with congenital syphilis tolerate bismuth better than mercury. The injections are also generally less painful. In neurosyphilis it is useful along with arsphenamine, and is sometimes valuable in tabetic crises, at least symptomatically; in general paresis, the results are poor. The *contraindications* are sepsis, severe nephritis (nonsyphilitic) and septic conditions in the mouth. Caution is indicated in diabetes, tuberculosis and hepatitis.

As prophylactic against syphilitic infection, bismuth is highly successful in rabbits, as long as intramuscular injections are continued (Levaditi *et al.*, 1926 to 1928). Efficient clinical protection by intramuscular injections of bismuth subnitrate in oil (1 cc. of 10 per cent weekly) has been reported (E. Sonnenberg, 1935). Hanzlik, Lehman *et al.*, 1940, suggest oral sobisminol.

Experimental Syphilis.—The antisyphilitic action of bismuth was first ascertained on rabbits. Eagle, 1938, showed that it is directly spirocheticidal *in vitro.* Levaditi, 1933, showed that the protective value correlates with the urinary concentration. Injecting a single large dose (100 mg.) as biliposol into a rabbit, he found it insusceptible to inoculation in ten days when the daily urinary excretion was 0.12 mg., but susceptible in thirty days when the excretion level had fallen to 0.012 mg.

Other Protozoan Infections.—Bismuth is effective against *frambesia,* although not so potent as arsphenamine (G. M. Saunders, 1937). In *Vincent's angina,* favorable results have been reported from one to three intravenous injections of thiobismol, in conjunction with the usual local treatment (Giese and Briskman, 1930). Bismuth is of slight value against experimental *trypanosome infections* (Sazerac and Levaditi) and recurrent spirillosis. The clinical dosage of the quickly absorbable thiobismol (0.2 Gm. intramuscularly) causes mitigation or temporary arrest of therapeutic *malaria.* This may be applied clinically to keep therapeutic malarial reactions under control. It acts more promptly than quinine, and enhances the effectiveness of this and of atabrine (H. N.

Cole *et al.*, 1940; C. E. Watson, 1939; Brunsting and Love, 1940). Other bismuth compounds do not easily reach the effective concentration level (W. F. Schwartz, 1939).

Administration.—In the treatment of syphilis, the bismuth preparations are administered by intramuscular injection, preferably into the gluteal muscles, since this appears to give better absorption (Cole, Farmer and Miskjian, 1926; Gruhzit, Tendick and Sultzaberger, 1927). In making the injection, "the needle should be inserted in the upper and the outer third of the buttocks, deep down into the muscular tissue; with the syringe tip inserted into the needle, the physician should aspirate back with the plunger of the syringe in order to be sure that the needle is not in a vein or in an artery. This will go far toward obviating many of the distressing venous emboli and arterial emboli that have been reported" (N.N.R.). The dosage is usually adjusted between 80 and 100 mg. of Bi per week, administered as a single weekly injection, with the suspensions and oil solutions; and divided into two or three injections for the watery solutions, to avoid excessive irritation. The injections are continued for six to ten weeks, unless stomatitis or other toxic effects appear. The bismuth is then intermitted for a month (or alternated with arsphenamine) before the course is repeated; this is especially necessary for the oil suspensions. *Intravenous injection* is practically precluded even for soluble bismuth compounds, since they tend to flocculate. Injection into the subcutaneous areolar tissue tends to form abscesses. *Oral administration* is ineffective except with sobisminol.

The *choice of the bismuth preparation* involves efficiency, local irritation and convenience. The close correlation of toxic and therapeutic action on intramuscular injection indicates that the potency in both respects is determined by the concentration of bismuth and not by the nature of the original compound (Longley, Clausen and Tatum, 1942). The potency can therefore be judged approximately by the *rate of absorption*, and this by the level of urinary excretion. Any preparation which maintains a urinary excretion level of 2 to 4 mg. of bismuth per day is potentially effective; levels materially above are potentially deterimental, depending upon how long they are continued. Temporary peaks of 10 to 15 mg. are apparently harmless. *Watery solutions*, such as sodium bismuth tartrate, iodobismitol or sobisminol and especially thiobismol, attain the effective levels most promptly, but decline so rapidly that they must be injected two or three times a week, which is painful and inconvenient. Oil suspensions of bismuth salicylate or sodium potassium bismuth tartrate reach the effective level slowly, generally by the cumulation of successive weekly injections which establish multiple absorption depots; but the effect is sustained correspondingly longer, and the weekly spacing is more convenient. Oily solutions are intermediate and should be injected every five to seven days (H. N. Cole, Sollmann, Henderson *et al.*, 1939). It is possible to combine the advantages and to avoid the disadvantages of the watery solutions and oil suspensions by administering a graded sequence of watery solutions(three injections in the first week, two in the second, one in the third, none after) during the early weeks of the suspension injections (Sollmann, Cole and Henderson, 1938).

Oral administration of sobisminol avoids the pain and inconvenience of the injections, and it can be made quite effective, but requires close supervision, including approximate estimation of the excretion level. A clinical method for this has been devised by Hanzlik, Lehman *et al.*, 1937.

The treatment of syphilis by oral administration of sobisminol was reviewed by the Council on Pharmacy and Chemistry, 1939, J.A.M.A., *113:* 2235. It is effective in patients as well as in rabbits, clearing the lesions about as rapidly as with intramuscular injections. Gastrointestinal upset is a frequent side action, sometimes so severe as to preclude its use. Stomatitis occurs occasionally. The *Sobisminol Mass* used for this medication is a complex organic bismuth product obtained by the interaction of sodium bismuthate, triisopropylamine and propylene glycol. It is marketed in capsules containing the equivalent of 150 mg. of bismuth. The adult dose is 2 or 3 capsules three times daily; a "course" extends over ten to twelve weeks.

Local Irritation and Pain.—The interaction of bismuth compounds with the tissues generally results in irritation and pain. Since the reaction is slow, the immediate pain is chiefly that of the trauma, even with the soluble preparations. It can be obviated by injecting a few drops of 1 per cent procaine solution. As the reaction proceeds, with the soluble preparations generally on the second day, somewhat later with the insoluble, there is more or less coagulation of the muscle fibers, edema, leukocytic infiltration and circumscribed necrosis (Gruhzit, 1929), with swelling, induration and pain, which may last for some days. The pain ranges from negligible to such severity that it has greatly restricted the use of the watery solutions. It varies not only with the sensitiveness of the individual, but also in the same person, according to the region involved and the spreading and the dosage of the injection. The smaller volume of concentrated solutions is an advantage. The addition of sugar diminishes the pain somewhat, perhaps because the viscosity hinders spreading. However, there is little difference practically between the various water-soluble preparations except that the rapidly absorbed thioglycollate (thiobismol) produces markedly less irritation, sensory or histologic (Gruhzit). With suspensions, the local changes may be more intense, but they develop so slowly, and are so much more circumscribed, especially with oil suspensions, that the discomfort is generally slight. Watery suspensions spread more freely and therefore are more painful; with the hydroxide, the irritation increases with the fineness of the particles, which promotes their solution (Lomholt, 1928). The reactions to the oil solutions have not been adequately studied, but the irritation is relatively slight.

Absorption, Distribution and Excretion of Injected Bismuth.—Success with bismuth requires the prolonged maintenance of maximal nontoxic concentrations of the active substance. The technic has been worked out chiefly by empiric trial, checked by studies of the absorption, distribution and excretion, clinically and in animals. *Studies on animals* should not be transferred too directly to the clinic, because of the differences in dosage as well as in the mineral metabolism; but when used with discrimination they lead broadly to the same conclusions. The absorption may be studied at the site of the injections, roughly by roentgen pictures and dissection, more accurately by the chemical determination of the remaining bismuth; and indirectly by the analysis of the excreta. The latter has the advantage that it can be done accurately *on patients;* and while it is not an absolute index of absorption, it reflects the concentration of actively circulating bismuth, which is of much greater practical, therapeutic and toxicologic importance than the fraction of bismuth which has been fixed in the tissues, for as with mercury, the patient relapses as soon as the excretable metal falls, and while considerable quantities are still unexcreted. Since there must be an equilibrium of diffusible bismuth between the tissues, the blood and the urine, the magnitude of the *urinary excretion* is determined directly by the concentration in the body. The few existing analyses of the blood indicate that the concentration of its bismuth is of a similar order of magnitude as that of the urine. The volume of the urine and the permeability of the kidneys doubtless have some effect on the excretion, but this appears of minor importance, altering only the detail, and not the general direction of the correspondence. The *fecal excretion* is variable and much smaller, generally less than a tenth of the urinary bismuth, but it follows the same direction.

The level of bismuth in the blood of patients receiving therapeutic intramuscular injections of water-soluble bismuth potassium saccharate attains 5 to 7 gamma per 100 cc. during cumulative administration. It goes fairly parallel to the daily urinary excretion; each gamma per day of urinary bismuth generally corresponds to approximately one gamma per 100 cc. of blood (M. H. Delp, Walker and Sondern, 1943).

The absorption of bismuth from intramuscular injection starts promptly and slows progressively, with considerable differences in the speed, duration and completeness for the various compounds. They depend chiefly on the solubility of the original compound or of its reaction products in the presence of tissue fluids; on the absorbing area, and therefore on the spreading of the injections; on the number and frequency of the injections; and on the dosage of bismuth. These differences determine both the systemic effects and the local actions, and therefore the clinical usefulness. The *solubility* is perhaps of the first importance in the speed and completeness of the absorption; however, the clinical solubility is not merely that in water, for *insoluble bismuth compounds* are gradually converted into soluble products, especially by interaction with the proteins, so that all bismuth compounds are "tissue soluble." The oily suspensions delay these reactions by restricting the contact; they are therefore liable to become encapsulated before absorption is completed. On the other hand, the *water-soluble compounds* tend to precipitate more or less rapidly on contact with the tissues, and then behave like the "insoluble" compounds.

Observations in the test tube and in the living eye (injection into the anterior chamber) show that the *precipitation* of the tartrate begins immediately, as it reacts with the *p*H and many ions of the tissue fluids; a part, however, remains in solution, so that the absorption is prompt as well as prolonged. The citrate is not precipitated by serum *in vitro;* in the eye also it does not precipitate immediately, but only after some hours, presumably by the dissociation of the sodium citrate through diffusion (von Oettingen, 1931). The sodium bismuth thioglycollate, because of its rapid absorption, appears least subject to precipitation in the tissues (Gruhzit, 1929).

Oily suspensions of water-soluble compounds are absorbed more slowly than their watery solutions, but more rapidly than insoluble compounds. The *oil solutions* have not been adequately studied as to their physicochemical reactions; but their absorption appears in general as good as or better than that of the watery solutions, slightly slower, but considerably more prolonged. The *absorbing area* depends on the spreading and on the number of the injections. Roentgen and anatomic studies (von Oettingen, Todd and Sollmann, 1927) show that the watery solutions spread in a thin sheet along the intermuscular fasciae, giving a large surface favorable to absorption and unfavorable to encapsulation. Oily solutions would probably spread in a similar manner. Suspensions, because of their viscosity, remain in large part in and near the track of the needle, offering a small surface and favoring encapsulation by local fibrosis (Mueller, 1922). With oily suspensions, diffusion is also hindered by the film of oil, until this is gradually broken down by the saponification and oxidation of fat. Mineral oils which do not undergo these changes allow the least absorption.

Repeated Injections.—The concentration of bismuth can be maintained at the effective level by repeated administrations, or by the establishment of depots of difficultly soluble bismuth for gradual mobilization. Both factors enter into the clinical use of all bismuth preparations, since the soluble compounds, with the possible exception of the thioglycollate, form precipitation depots; so that weekly injections suffice to maintain the concentration. Repetition of the injections does not merely replenish the concentration, however, but results in marked progressive increase in the concentration, as reflected in the excretion level, almost proportional to the number of injections; *i. e.*, after ten injections, the weekly excretion level would be over five times as high as after a single injection. This holds for all the compounds, and may be attributed to the increased absorption area. The repetition of the injections therefore amounts not merely to prolongation, but to intensification of the dosage and action.

The thinning of the *roentgenographic* shadow at the site of the injections does not distinguish sharply between absorption and spreading. It is therefore especially unreliable for aqueous solutions; but even with the suspensions, it is difficult for comparisons. For instance, in the clinical studies, quoted in von Oettingen's review, the shadow of the tartrate-oil injections had disappeared with some patients in a week, in others not even in seven months; with some salicylate-oil injections, the shadow was gone within a month, with others it was still present after a year.

Chemical analysis of the site of the injection gives quantitative data, but sacrifices the animals with one determination, so that the further course of the absorption cannot be followed. However, it permits comparison of different compounds. Using dogs (which seem more suitable than rabbits for this purpose), generally forty-eight hours after intramuscular injection of the full clinical dosage, the ranking of the various bismuth preparations correlates well with that of the clinical excretion studies, with few exceptions. Bismuth thioglycollate is practically completely absorbed in two hours; the others are incompletely absorbed at this time, 30 to 80 per cent for watery and oil solutions, 20 to 22 per cent for suspensions. The absorption proceeds actively for more than three hours, and much more slowly after eighteen hours, when there is still considerable unabsorbed. If the compounds are arranged in the order of absorbability (the reciprocal of the amount unabsorbed at forty-eight hours), thiobismol stands alone in the highest rank; other watery solutions are in the second and third rank; oil solutions in the second, third and fourth ranks, and oil suspensions are all in the fourth or lowest rank. Increase of dosage increases the amount of bismuth absorbed, but the percentage absorbed is not materially altered by doubling the dosage (Sollmann and Henderson, 1938).

The clinical urinary excretion, which reflects the level of the therapeutic effect, has been studied especially by Lomholt, by Hanzlik and his associates, and by Sollmann, Cole and Henderson, for its general course and for the comparison of the various bismuth preparations. The studies have given concordant results, although the details vary according to the difference in the administration. In general, with the ordinary clinical dosage, the urinary excretion reaches 2 to 8 mg. on the peak day; the weekly excretion ranges between 4 and 40 mg.; the total urinary excretion is between 15 and 50 per cent of the amount injected; the fecal excretion is 0.6 to 4.5 per cent of the injection, except for iodobismitol (to 18 per cent) and thiobismol (to 35 per cent); between one-third and nine-tenths of the injected bismuth is retained at the site of the injection and in the organs.

Single injections give the simplest picture of the *excretion curve;* repeated injections differ only by starting from progressively higher levels with succeeding injections. The excretion begins promptly, but varies in steepness of ascent, according to the absorption velocity. The thioglycollate stands at one extreme, with rapid ascent and descent of the curve; the subsalicylate at the other, with slow rise and prolonged descent. The other preparations are intermediate, with the watery solutions nearest to the thioglycollate, and the oil solutions somewhat nearer the suspensions. There is considerable overlapping, however, and the differences between individual patients are often greater than the differences between preparations. In general, the *peak* is sharp with the watery solutions, and is attained on the first to third day; with the oil solutions it is reached about the fifth to tenth day; suspensions do not have a sharp peak, but reach their maximum about the twelfth day after the injection.

The *steepness of the descent* decreases with the duration of the absorption. Since it forms a logarithmic curve without sharp end point, the rapidity of the descent may be compared by the time when it has fallen to half of the peak level. For a given preparation, this is reached in practically the same period from a high and from a low level, whether the injection was single or multiple; with watery preparations, about the second day after the last injection; with oil solutions, about the fifth day; with suspensions, about the tenth day. The *percentage* of the injected amount of bismuth excreted in a given time is a fairly constant characteristic of each preparation, largely independent of the amount injected, whether one or multiple injections, depending largely upon the rate of the absorption, varying therefore somewhat for each patient. With the clinical dosage, at the end of three weeks, the urinary excretion amounts to nearly 50 per cent of the injection for iodobismitol, 15 to 30 per cent for other watery solutions, oil solutions and tartrate suspension, and about 5 per cent for salicylate suspension. *The total amount of bismuth retained* at the end of three weeks of clinical injections (subtracting the urinary and fecal excretion from the total quantity injected) amounts to 73–258 mg. of bismuth, median about 180 mg., for all preparations, the grouping being rather immaterial.

The *amount excreted* depends upon the absorbability of the preparation and upon the amount injected at one time and in the entire course. The level reached at the peak represents intensity of action; the weekly or total excretion shows sustained action. Both are probably concerned in the therapeutic effect, and clinical data are not yet sufficient to decide which is the better index. The rapid absorption of the thioglycollate gives it a unique position, reaching the highest peak of about 0.85 mg. of Bi per hour, three hours after intramuscular injection corresponding to 75 mg. of bismuth, but only for a short time. To sustain such a level would presumably soon become dangerous. For the other preparations, the *peak excretion* may be figured for twenty-four hours. In the third week of treatment with the ordinary clinical dosage they run about 6 mg. for the watery solutions; 2 to 6 mg. for oil solutions; 3 to 3.5 for tartrate suspension; and about 1.2 for salicylate suspension. *Continued action* is perhaps best reflected in the average daily urinary excretion of the third week, which is near the middle of the course, and therefore presents an approximate average of the whole. For the clinical dosage, this amounts to 5 to 5.5 mg. for watery solutions, 2.5 to 3.5 for oil solutions, 1.5 to 2.5 for tartrate suspension and about 0.7 for salicylate.

Late Bismuth Excretion.—When the injections of bismuth cease, the daily excretion descends as a parabolic curve, which is steeper for high than for low excretion levels. When it reaches 1 mg. per day, it has become practically horizontal, and continues about this level indefinitely, at least over half a year, through the gradual remobilization of bismuth that had been deposited in the tissues (Sollmann, Cole and Henderson, 1937). This has no therapeutic effect.

The *fecal excretion* of bismuth constitutes a relatively small proportion of the total excretion, 4 to 10 per cent with oil solutions, 6 to 22 per cent with watery solutions, 12 per cent with oil suspensions. With thiobismol, however, it averages 56 per cent of the total excretion. Its relation to the blood concentration is less direct than the urinary (Sollmann, Cole and Henderson, 1937).

An unusually large but nonfatal dose of bismuth salicylate (equivalent to 675 mg. of bismuth, nine times the ordinary amount, by a single intramuscular injection) was followed by the urinary excretion of 246 mg. in two weeks; the daily peak was 16 mg. (J. Seifter and McDonald, 1943).

Excretion studies in animals are significant chiefly for toxic doses. *With relatively enormous doses, in rabbits,* Leonard, 1926, recovered 2 to 10 per cent from the urine when death occurred within a week, and up to 33 per cent within two weeks. These severe intoxications, which include marked nephritis, have little relation to the clinical conditions. These limitations apply also to the studies of Gruhzit *et al.* on dogs. The latter, however indicate that the fecal excretion in such dogs is considerably higher than under clinical conditions. According to the Thiry fistula experiments of Bargen, Osterberg and Mann, 1929, considerable bismuth is excreted directly into the colon of dogs, after intravenous injection of the sodium citrate.

The *absorption and excretion with oral administration* of most bismuth preparations is too small and uncertain for syphilis therapy. However, *sobisminol*, a soluble preparation derived from sodium bismuthate, is absorbed more liberally, promptly and with fair uniformity (Hanzlik *et al.*, 1936, 1937; confirmed by Sollmann, Cole and Henderson, 1937) so as to give urinary excretion curves resembling closely those of intramuscular injections of watery and oil solutions, in degree and in course, and to produce equally satisfactory therapeutic results. The dosage, however, must be considerably higher (420 mg. of Bi daily), as only a fraction is absorbed, the urinary excretion amounting to about one-half per cent of the quantity administered.

Rectal absorption of bismuth was claimed for a bismuth salt of heptadiene carboxylic acid (diallyl acetic acid); but no bismuth was found in the organs of patients who died as a result of the suppositories, death being due apparently to the hydrocarbon (J.A.M.A., 1947, *133;*962).

The **organ distribution of the retained bismuth** in autopsies from patients who underwent clinical treatment, and in dogs sacrificed forty-eight hours after intramuscular injection of clinical doses, is much like that of other metals, with a still greater predilection for the kidneys. The liver ranks next, but at some distance; it contains relatively more with chronic than with acute administration. The chief factor in the bismuth concentration in clinical cases is the total dosage. About half of the retained bismuth is excreted in the first three weeks after the administration is stopped. The remainder is retained tenaciously. These factors affect all organs similarly, and the distribution of the different preparations appears identical. Newborn infants whose mother had been treated show the same concentration as adults, so that the bismuth passes freely across the placental circulation (Sollmann, Cole and Henderson, 1938). Passage into the amniotic fluid had been reported by Kraul and Bodmer, 1926. Leonard and Love, 1928, found the distribution in the fetus similar to that in the adult. Bismuth is also excreted into the milk, but in lower concentration than in the urine (Cordaro, 1934; von Kennel, 1931).

The clinical series of Sollmann, Cole and Henderson comprised twenty-two patients who had received courses of bismuth, generally the salicylate, and three newborn infants of such patients. The median concentrations, as mg. of Bi in 100 Gm. of undried tissue were (in descending sequence): kidneys, 3.33; liver, 0.68; bile, 0.39; spleen, 0.155; ileum, 0.118; colon, 0.115; lungs, 0.085; jejunum, 0.083; brain, 0.06; blood, 0.05. If the total amount or bismuth administered is materially greater or less thay 750 mg., the average content varies in simple proportion. Dosage and time affect the storage similarly in all the viscera, including the blood. Some individual data differ considerably from the median, often without apparent reason. The *total amount of bismuth stored* in the body was calculated as 4 to 770 mg., median 82 mg., about 7.4 per cent of the amount administered. The liver and kidney each contained about a ninth of the total. The metal concentrations of the organs in clinical *poisoning by mercury and lead*, acute or chronic, fell within the range of the bismuth concentrations; the medians are about a third lower for chronic mercury and lead poisoning and three or four times higher for acute. The kidney ranks conspicuously highest for bismuth and mercury concentration, not especially high for lead. The liver ranks highest for lead, second for mercury and bismuth, but the latter at a considerably lower level. The spleen has its highest concentration in acute lead, next in acute mercury. The intestines are lower than the spleen and the lungs rank relatively low in all. The brain is generally of the same order of magnitude as the lung and a fifth to three-fourths higher than the blood, which is relatively low in all.

Distribution studies on animals permit changing the experimental conditions, particularly to compare different preparations. It was found, however, that the distribution of various types of preparations is similar forty-eight hours after the clinical doses have been injected into dogs. This holds for the oil-soluble as well as for the water-soluble compounds, and for the brain as well as other organs. Although these experiments were much shorter than the clinical administration, the bismuth concentration in the various organs fell within the range observed in the human patients and ranked in the same order, with the notable exception of the liver, which averaged distinctly higher, approaching the kidney concentration, indicating that the liver bismuth accumulates slowly. The retention by the tissues was found relatively more efficient for smaller than for larger quantities of absorbed bismuth. The total quantities retained in the tissues under these conditions (forty-eight hours after injection) was calculated as nearly two-thirds of the quantity actually absorbed from the injections (Sollmann and Henderson, 1938).

With intravenous injections, the bismuth leaves the blood rapidly, following a parabolic curve. The kidneys and lungs store it more rapidly than the liver and spleen (Sollmann and Seifter, 1941). With flocculating preparations, relatively larger quantities are retained in the reticulo-endothelial system, liver, spleen and lungs (E. Frankel, 1923).

The published data on the *distribution after toxic doses* are reviewed by Forst, 1935, in Heffter's Handbuch der exper. Pharmakol., Vol. 3, part 4. *The bismuth concen-*

tration of the brain and cerebrospinal fluid has been especially investigated with a view to the treatment of neurosyphilis. The brains of animals have not shown any distinctive differences for the various preparations (Sollmann and Henderson, 1938), and the available analytical methods are not reliable for the small quantities found in amounts of cerebrospinal fluid that can be collected.

Bone.—It is doubtful whether bismuth is concentrated in trabecular bone analogous to lead. Anatomical changes in bone have been described as the result of bismuth injections in children and in puppies (Caffey, 1937), and osteoporosis has been reported in adults (Racouchot, 1939). These need not be due to bismuth concentration, but may be more analogous to the bone changes produced by arsenic. Similar changes have been reported in the long bones of fetus if the mother received bismuth injections during the time of her pregnancy (J. Whitridge, 1940).

Tumor tissue was reported to show selective deposition of bismuth, and it was suggested to use the bismuth isotope, Radium E, to localize radiation in the tumors (Zadik, 1931).

Precipitation of Bismuth Sulfide.—Bismuth forms a black and insoluble sulfide. Since H_2S is always present in the large intestine, the feces are colored black when absorbed bismuth is circulating in the blood; this precipitation also occurs in and around the capillaries in situations in which hydrogen sulfide is formed by putrefactive processes. The black blotches are characteristic around the alveolar margin of the gums ("bismuth line") and the adjacent mucosa and tongue (Warfield, 1912); in the colon, rectum, cecum and appendix (none in the small intestines); in the urinary bladder if this is infected with coli; rarely in the reticular layer of the skin (Lueth, Sutton *et al.*, 1936). It gives rise to some stomatitis; and in severe poisoning to capillary embolism and ulceration of the large intestine, with the clinical symptoms of vomiting, diarrhea, cramps, colic and colitis—the latter rarely as severe as with mercury (Cabot, 1912). Bismuth has been demonstrated spectrographically in the gum margin (R. Probst, 1932).

M. Wachstein and Zak, 1946, found bismuth discoloration of the colon in about 1 per cent of consecutive routine autopsies.

The form in which bismuth is present in the tissues is imperfectly known. The serum bismuth appears united with the protein, since it can be salted out with all the fractions and does not pass ultrafilters (Lomholt's review, p. 243); but formation of bismuth sulfide deposits indicates that it is ionized. That stored in the tissues is largely nonionized, for histochemical methods fail when destructive methods show considerable bismuth (Levaditi and others). The *histologic demonstration of bismuth* in organs is discussed by H. Brabant, 1941; Castel's method, 1936, is described by Wachstein and Zak, 1946. Renal cells contain refractile granules which give equivocal bismuth tests (Pappenheimer and Maeckling, 1934). Levaditi and Nicolau, 1924, assumed the formation of a hypothetical "*bismoxyl*" because the toxicity of bismuth for trypanosome and spirillosis cultures appeared increased by incubation of bismuth with extracts of organs (especially those rich in glutathione, Levaditi and Howard, 1929; not with serum). Fournier *et al.*, 1929, attempted to apply the idea clinically, but the observations seem to lack adequate confirmation.

Diuretic Action.—Clinical injections of bismuth tend to produce some diuretic effect, analogous to mercury, but generally not so extensive (Mehrtens and Hanzlík, 1928; Hanzlik, Bloomfield *et al.*, 1929). This is also seen in dogs, with injection of 1 to 4 mg. of bismuth ammonium citrate per Kg. (Kisch, 1934).

Toxic Effects.—Because of the limited gastro-intestinal absorption, oral administration does not lead to toxic bismuth effects, even if continued over long periods. Large doses of the subnitrate, however, may give rise to nitrite poisoning. Serious and sometimes fatal poisoning, presenting the features of subacute or chronic arsenic, mercury and lead intoxication, may occur with the injection of large doses into closed cavities, and with extensive application to burns. The literature was reviewed by J. Phillips, 1917. With the gradual dosage of intramuscular injection in syphilis therapy, serious phenomena are rare, if the administration is stopped with the first warning symptoms. In animals, functional and histologic renal injury requires doses equivalent to more than nine times those used in human therapy (H. Brown, Saleeby and Schamberg, 1926). The therapeutic dosage may produce foul breath, *black "lead line"* at the alveolar margin and sometimes black spots on the buccal mucosa and throat; and annoying but not serious *stomatitis.* These phenomena usually occur when the total dosage reaches 2 to 2.5 Gm., but occasionally even with 0.5 Gm. The gum line is said to be present in practically all patients who have had six or more injections (J. E. Moore). Salivation is relatively less than with mercurial stomatitis. The administration should be stopped when gingivitis appears. A blue gum line is not a contraindication. The black discoloration generally fades in two to three months. Blue generalized *discoloration of the skin* resembling argyria has been described, but is rare.

If the warning is not heeded and the bismuth is continued, serious ulcerative stomatitis is likely to result, and other toxic effects develop: *malaise* (nausea, loss of appetite, loss of weight, headache, sleeplessness, depression, asthenia, joint pains); *diarrhea; albuminuria; skin reactions* (pruritus, herpes zoster, purpura); sometimes serious exfoliative dermatitis and rarely *jaundice. Conjunctival hemorrhage* is a rare sequel of bismuth injection (E. L. Cohen, 1945). The mouth, digestion, skin and urine should be watched, and the bismuth stopped with the first sign of disturbance. These precautions render bismuth treatment practically safe. Oral hygiene should be prescribed, to prevent undue stomatitis. In any case, the stomatitis is usually less severe than that of mercury, the cutaneous eruptions are more rare than with arsphenamine, and milder and renal irritation (albuminuria) is less frequent than with mercurials. If bismuth symptoms develop with *Beck's paste*, this should be removed with warm olive oil, curetting if necessary (Zollinger, 1912).

In a series of 2750 patients who had received courses of bismuth injections, recorded by Brittingham, 1933, thirty developed stomatitis, three watery diarrhea and two renal symptoms. *Jaundice* is rare; the patients recorded by Nomland *et al.*, 1938, all recovered and were subsequently again treated with bismuth, without harm. *Fatalities* recorded in the literature (Beerman, 1932) comprise six acute deaths from intravenous injections, and seventeen delayed deaths in which the share of bismuth is somewhat doubtful.

The *toxicity for rabbits* was investigated by Sazerac and Levaditi, 1921. Intravenous injection proved fatal in a few days with the dosage of 5 mg. of the potassium bismuth tartrate per Kg., but with intramuscular injection 60 mg. per Kg. was well tolerated, 100 mg. was toxic and 200 mg. was fatal in four days. The histologic lesions involve mainly epithelial degeneration of the convoluted tubules of the kidneys and cloudy swelling of the liver cells Lucke and Klauder, 1923). The toxicity and urinary elimination of various bismuth preparations was studied by C. L. Leonard, 1926, and the toxicity for rabbits by Raiziss *et al.*, 1934. The *speed of intravenous injection* influences the fatality; slow injections nearly double the tolerated dose. Acute deaths present the phenomena of flocculation; delayed deaths those of uremia, without cerebral symptoms (Sollmann and Seifter, 1941). Slow-drip injections are about twice as toxic to rabbits infected with syphilis. This is apparently related to the lower ascorbic acid content of their blood. The largest doses that were survived were ineffective against the syphilis (F. P. Ludueña, 1943). The prompt fall of blood pressure by the intravenous injection of soluble bismuth salts was described by Meyer and Steinfeld, 1885, who considered it analogous to that of arsenic. In contrast to this, however, the bismuth fall is generally followed by prompt recovery, if it is not immediately fatal. It closely resembles the fall produced by other flocculating agents, including most metals. According to G. A. Masson, 1926, it is chiefly cardiac, owing to disturbed conduction and heart block, which may also be produced in perfused hearts.

Trimethyl Bismuth $Bi(CH_3)_3$, volatilizes readily and oxidizes easily to bismuth oxide. It is a very active poison when administered by inhalation, or orally, or through the intact skin. It produces inflammatory reactions (vasodilatation, edema, extravasation, necrosis and ulceration) on local application to the skin and mucous membranes; and after absorption or parenteral administration, in the lungs, gastro-intestinal tract and kidneys. It has little or no effect on nonvascular structures, such as the cornea. These characteristics resemble those of arsenic, and it also causes a similar gradual fall of *blood pressure*. Acutely fatal doses paralyze the cerebral centers, partly at least by aliphatic narcosis. Repeated administration of sub-lethal doses leads to marked *encephalopathy* resembling lead poisoning. Very dilute solutions depress excised smooth muscle and the excised heart. Even saturated solutions have little effect on skeletal muscle and motor nerves and endings. The kidneys in acute poisoning contain relatively less bismuth than with ordinary bismuth compounds. *Triethyl bismuth* resembles the trimethyl in all respects but is unmanageable because it is spontaneously inflammable (Sollmann and Seifter, 1939).

Bismuth Compounds Used in Syphilis Therapy.—Practically all the numerous compounds introduced for this purpose are effective when properly administered (in courses of ten weeks, alternating with arsphenamines). The practical differences are in the rapidity of absorption, which governs the frequency of administration and tendency of cumulative effects, which in turn depends on the solubility of the compounds and the medium in which they are administered. This brings them under the following groups:

Aqueous solutions of anionic bismuth salts of complex composition. The solvent may contain sugars, glycerin or glycols. They must be administered about twice weekly, in doses corresponding to about 33 mg. of Bi per injection. Sodium bismuth thioglycollate, *thiobismol*, is by far the most quickly absorbed and the most quickly excreted (Gruhzit *et al.*). *Sobisminol* (sodium bismuthate derivative) probably ranks next in absorbability, but at some distance. It is also active by oral administration, in capsules, but this requires much larger doses (Hanzlik *et al.*, 1937, 1938, 1939; report, Council on Pharmacy and Chemistry, 1939, J.A.M.A., *113:* 2235). Iodobismitol (sodium iodobismuthite) has about the same rank for intramuscular injection, but is not suitable for oral administration (Hanzlik *et al.*, 1932; Gurchot *et al.*, 1932; C. C. Johnson *et al.*, 1932). *Potassium bismuth tartrate* is marketed as a solution in 40 per cent sucrose. *Sodium bismuth citrate* was investigated extensively by Sollmann *et al.*, but was deemed to cause too much local induration. *Oily solutions* include basic bismuth salts of certain large-molecule organic acids (biliposol, bismo-cymol) and quinobine, an oil-lecithin solution of bismuth iodoquinate. These are injected every fifth to seventh day. *Oil suspensions of water-soluble compounds*, especially the potassium bismuth tartrate, may be injected every three to seven days, in doses of 0.1 to 0.2 Gm. Settling of suspensions may cause considerable inexactness of dosage (Cole *et al.*, 1931). *Oil suspensions of insoluble (or sparingly soluble) compounds*, bismuth salicylate (subsalicylate), iodoquinate (quinby), benzoate and oleate and metallic bismuth. The salicylate is used extensively for sustained effects; they are mild at first, but become cumulative. It is injected weekly, generally 0.13 Gm., which attains a urinary excretion of 1 mg. per day in about three weeks. By using 0.26 Gm., a urinary level of 2 mg. per day is attained in one week (Sollmann, Cole and Henderson, 1938). *Watery suspensions of insoluble compounds*, hydroxide (Lomholt's magma), metallic bismuth (neotrepol), and semicolloidal bismuth (bismol). These are rarely employed in this country.

PREPARATIONS.—Bismuth compounds are generally *incompatible* with mercuric chloride, tannic acid, iodides and sulfur.

***Bismuth Potassium Tartrate,** U.S.P.; a basic bismuth potassium bismuthotartrate, containing about 61 per cent of bismuth. Granular white powder, freely soluble in water (1:2). Dose, 0.1 Gm., intramuscularly. *Bismuth and Potassium Tartrate Injection*, U.S.P., may be prescribed either as *Aqueous Solution*, 30 and 60 mg. in 2 cc., or *Oil Suspension*, 100 and 200 mg. in 2 cc.

***Bismuth Subcarbonate,** U.S.P. (Bismuth Oxycarbonate), yields not less than 90 per cent of Bi_2O_3. White powder; odorless and tasteless. Insol. in water or alc. Dose, 1 Gm., 15 grains; in powders or suspension. *Bismuth Subnitrate*, U.S.P., has similar properties. *Bismuth Subgallate* (Dermatol), yielding not less than 52 per cent of Bi_2O_3, is an amorphous, bright yellow powder, odorless and tasteless. Insol. in water or alc.

***Bismuth Subsalicylate,** U.S.P., yields about 64 per cent of Bi_2O_3. A white or nearly white, amorphous or crystalline powder; almost insol. in cold water. Dose, gastro-intestinal, 1 Gm., 15 grains; anti-syphilitic, 0.125 Gm., 2 grains, by intramuscular injection of 10 per cent suspension in oil. *Bismuth Subsalicylate Injection*, U.S.P., in oil; usual sizes, 100 mg. and 120 mg. in 1 cc.

Iodobismitol with Benzocaine, N.N.R., a solution of sodium iodobismuthite, N.N.R. *Dose*, 2 cc. (containing 25 mg. of bismuth), intramuscularly every three days for 16 to 20 injections.

Sobisminol Mass, N.N.R., a complex product obtained by the interaction of sodium bismuthate, tripropanolamine and propylene glycol. Marketed as capsules of 0.75 Gm. containing 150 mg. of bismuth. *Dose*, two or three capsules three times daily for ten to twelve weeks. *Sobisminol Solution* contains about 20 mg. of bismuth per cc., dissolved in a mixture of propylene glycol and water. *Dose*, 2 cc. twice a week, intramuscularly.

Thio-Bismol, N.N.R., sodium bismuth thioglycollate, chiefly Bi $(SCH_2CO_2Na)_3$, containing about 38 per cent of bismuth. A yellow granular substance, freely soluble in water, but solutions are unstable. Marketed in ampuls of 0.2 Gm. Dose, 0.2 Gm. intramuscularly three times per week for twelve to fifteen doses. A single injection arrests therapeutic malaria temporarily.

◆

IRON

Iron occurs widely distributed in the body, in several more or less firm and nonionizable combinations. It is found in all chromatin and therefore in all cells; in hemoglobin of the blood; and in granular form as "reserve iron" in the blood-forming and destroying organs. It is important chiefly in relation to blood formation. When administered to normal animals, it has no systemic action, but increases the "reserve iron." In most anemias, the administration of iron tends to restore the hemoglobin to the normal and therefore improves nutrition. The soluble ionizable salts exert local astringent effects.

Direct systemic actions may be secured by the intravenous or hypodermic injection of nonprecipitating salts, or by the absorption of corrosive preparations. The effects resemble those of arsenic (H. Meyer and Williams, 1881; Jacobj, 1887). Toxic effects occur with 60 mg. per kilogram, hypodermically or by vein, but not with therapeutic hypodermic doses (Lépine, 1897). E. J. Stieglitz, 1921, found that injected iron is deposited party in the kidneys, and that this is midly nephrotoxic. The *intravenous toxicity* is due largely to flocculation. The double salts are not directly precipitant, and therefore are much less toxic than the simple salts (Sabbatini, 1926). Even ferric chloride, however, can be injected by vein without harm, if it is diluted to 0.25 per cent. In rabbits infected with tuberculosis, it accumulates in the *tuberculous tissue* and appears to retard the progress of the disease. Menkin, 1937, injected 20 to 30 cc. of a 0.0625 per cent solution in isotonic saline, two or three times a week, for over a hundred injections into patients with advanced tuberculosis, without untoward systemic effects, although there was sometimes temporary local thickening of the vein.

Intravenous injection of calcium salts protects mice against intravenous fatality of iron salts, but fails in rats and rabbits (E. Rothlin and Schalch, 1946).

Astringent Action and Uses.—The soluble salts, especially the ferric, precipitate proteins readily and are therefore styptic, astringent, irritant and even corrosive. The Tincture of Ferric Chloride is employed as an astringent, especially in gargles (1:10), but discolors and corrodes the teeth. This and other iron salts, particularly the Iron Subsulfate Solution, are used as local styptics for capillary bleeding; but the efficiency of coagulant astringents in hemorrhage is low, even under favorable experimental conditions (Hanzlik, 1918), and they are likely to devitalize the wound and impede repair. In *ringworm*, Garrett, 1913, recommended painting the scalp with undiluted Ferric Chloride Solution.

In the alimentary tract the local actions of iron salts may produce some gastric irritation, usually mild, and sometimes diarrhea or constipation. The stools turn black through the formation of iron sulfide.

Large Doses on Phosphate Metabolism.—Continued feeding with large doses of ferric salts (as also of alum) to guinea pigs or rabbits precipitates the alimentary phosphate in the digestive tract and prevents its absorption, and thus lowers the blood phosphate (to 15 per cent of the normal) and reduces the ash calcium and phosphorus of the bones; the urinary excretion of phosphate almost ceases. These effects can be prevented by adding an excess of phosphate to the diet (G. J. Cox *et al.*, 1931). Similarly, 2 per cent of reduced iron, which has no effect when added to the normal diet, produces, when added to a rickets-producing diet, anemia and retardation of growth, and these effects are counteracted by vitamin D (K. Waltner, 1929).

Income and Output of Iron.—The body of an adult man contains about 3 to 3.5 Gm. of iron, of which about 2.4 to 2.7 Gm. are in the form of hemoglobin (mammalian hemoglobin contains 0.34 per cent of iron; blood about 50 mg. per 100 cc; plasma about 0.5 mg. per 100 cc.). On a normal diet, he excretes daily about 20 mg. of iron; even in starvation the excretion averages about 8 mg. (Cetti and Breithaupt, 1893). This is normally replaced by the absorption of iron from the food. The iron content of the ordinary daily American diet may vary between 7 and 35 mg., generally between 11 and 19 mg., 16 mg. being the mean value. This amounts to about 1/200 of the total iron of the body, and is ordinarily about twice the minimum requirement. It is more than sufficient even in otherwise poorly nourished individuals, since vegetable diets are relatively rich in iron and 90 per cent of this is "available," in contrast to less than half for meats. However, the iron income may fall much lower on restricted and "freak" diets; Exclusive "tea and toast" may lower it to 2–5 mg. White bread is poor in iron; cow's milk contains 0.5 mg. per liter, so that it would require 20 liters to supply 10 mg. of iron (Sherman, 1907; extensive bibliography).

Iron Equilibrium.—Various careful investigations concur that this is attained in adult men or women with a minimum dietary income of 5 to 8 mg. (Retznikoff *et al.*, 1934; Farrar and Goldhamer, 1935; Vahlteich *et al.*, 1935). Doubling this income does not create a positive balance, unless an iron debit exists, as in anemia. Otherwise, the excess is merely excreted or not absorbed (McCance and Widdowson, 1938). The loss of iron in menstruation is not sufficient to affect the balance. Pregnancy, however, requires a larger income, 15 to 20 mg. per day (Coons and Coons, 1935). Young children also require more iron, but 0.6 mg. per Kg. per day, equivalent to 40 mg. for adults, should suffice for normal growth and maintenance (M. S. Rose *et al.*, 1930; A. L. Daniels and Wright, 1934).

The *loss in a menstrual period* is from 6.6 to 180 cc. of blood, 0.7 to 23.6 Gm. of hemoglobin, 2.3 to 79 mg. of Fe. The majority, however, range between 20 and 30 cc. of blood, 3 and 6 Gm. of hemoglobin, 10 and 15 mg. of Fe; divided by twenty-eight days this gives ⅓ to ½ mg. of Fe per day, 0.1 to 0.15 Gm. of hemoglobin (L. H. Gilette *et al.*, 1918; Ohlson and Daum, 1935; Vahlteich *et al.*, 1935; Barer and Fowler, 1936).

The *normal hemoglobin level* is maintained for long periods with an iron income of 5 mg. per day (Farrar and Goldhamer, 1935), and only a part of this, perhaps a third, is absorbed and *utilized.* Lintzel's work (1929) suggests that the actual utilization of iron in normal adults may be somewhat less than 1 mg. per day. Large increase of iron income by the administration of ferrous iron, the form best utilized, scarcely alters the hemoglobin of males; that of women in England, which is often somewhat low, is raised by 4 to 17 per cent (Widdowson and McCance, 1936). Healthy young women who for three to eight months consumed controlled diets with a daily iron income of 6.55 mg., averaged a daily retention of 2.14 mg., so that 6.5 mg. is more than adequate: 4.5 mg. led to iron loss (R. M. Leverton, 1941).

The **utilization of iron,** its absorption, storage and conversion into hemoglobin, are closely adapted to the needs of the organism. Income in excess of that needed to maintain normal hemoglobin level is eliminated by the feces without being absorbed, except for a small fraction which is added to the reserve stock of iron laid down loosely bound in granules within the cells, especially of the liver and spleen. If the hemoglobin level is low, however, iron is freely absorbed and is built promptly and directly into hemoglobin. In any case, the absorption appears to occur only as dissolved ionized iron, which can exist only as ferrous iron salts in the duodenum; other iron compounds are changed into this form in digestion, but only in part, so that larger quantities must be taken to secure the same absorption. Reduction and oxidation of iron occur readily and the absorbed iron circulates in the plasma in ionic form, probably ferric. In the organs it is again reduced to ferrous. The synthesis into hemoglobin is a more complicated process.

Historical.—The study of the utilization of iron has been complicated by the fundamental difference between the normal and anemia; by the small quantities involved in the normal utilization; and by theoretical preconceptions of the implications of synthesis of a protein from an inorganic element in the animal organism. The treatment of anemia with iron was practiced in antiquity and probably had a symbolic origin, the patients drinking water in which swords had been allowed to rust, with the idea that the strength of the steel would pass into the patient. However, Celsus (about 25 A.D.) advised to treat enlargement of the spleen by drinking the water in which the glowing iron is drenched in the smithies (and which presumably contains colloidal iron oxides), because, he avers, domestic animals raised about smithies, that drink this water, have abnormally small spleens ("quod animadversum est in his animalibus, quae apud hos fabros educata exiquos lienes habent;" liber IV, Cap. IX). With the discovery of the presence of iron in the blood (Menghinis, 1746), the therapeutic results seemed to be easily explained on the assumption that the iron is absorbed and converted into blood, much as the nitrogen of food is converted into muscle; but when the earlier experiments failed to show absorption of the medicinal iron preparations, some writers became skeptical of the clinical results; others (especially Bunge, 1885) were inclined to attribute them to the local actions of iron in the alimentary canal. There could never be any question that iron is absorbed from food, for the hemoglobin increases with the growth of the animal. The same was conceded for certain organic irons, and Macallum (1894) and Hall (1896) studied their absorption by microchemic methods. The absorption of inorganic iron was also proved, but it was objected that the iron had produced corrosion; when this criticism was found inadequate, it was claimed that inorganic iron, while it is absorbed, cannot be converted into hemoglobin (Abderhalden, 1899), but that it is nevertheless beneficial in anemia, by stimulating the blood-producing organs to a better use of the organic irons. This objection was also found untenable and abandoned (Abderhalden, 1906).

The **absorption of iron** occurs mainly from the duodenum, but somewhat also, in decreasing order, from the succeeding portions of the intestine. A part generally escapes absorption and is eliminated by the feces. The part which is absorbed passes into the intestinal epithelium in a dissolved condition, and then directly into the capillaries, not by way of the lymph (C. V. Moore *et al.*, 1939). With anemic dogs, radioactive iron appears in the red corpuscles a few hours after oral administration (P. F. Hahn, Bale *et al.*, 1939). In the meantime, it passes presumably into the maturing cells of the bone marrow.

Radioactive iron furnishes the best means of following the absorption and further fate of administered iron. This is identical for ferrous and ferric salts. In either case, normal dogs with adequate iron store absorb little if any, 0.08 to 0.24 mg.; but dogs rendered anemic by repeated severe hemorrhages absorb 4.1 to 12.7 mg., about fifty times as much as the normal dogs. The iron absorption from the gastro-intestinal tract appears to be controlled by the level of the reserve stock of iron, or more directly, by the level of ferritin in the intestinal cells; and not by the level of hemoglobin.

The increased absorption does not occur when the hemoglobin is lowered by pernicious anemia, hemolytic neoplasms or infectious anemias (P. F. Hahn, 1945). In pregnancy the absorption is high, although the hemoglobin level may be normal; polycythemia has normal absorption (W. M. Balfour *et al.*, 1942). In acute hemorrhage, the increase sets in only when the reserve stock becomes deficient, after twenty-four hours to seven days (Hahn, Ross *et al.*, 1943).

Subcutaneous aseptic (turpentine) abscess decreases the absorption of iron from the digestive tract of anemic dogs from 41 to 4.1 per cent of the ingested dose (Hahn, Bale and Whipple, 1946).

The control of the absorption is situated within the intestinal tract, for the anemic absorption is soon inhibited by oral administration of iron, but not by intravenous injection (G. E. Sheline *et al.*, 1943).

P. F. Hahn, Bale *et al.*, 1943, believe that the intestinal mucosa becomes saturated by the iron that is fed, so as to prevent further absorption until this has been passed on to the reserve stock. They suggest that the blocking of the mucosal cells is through loose combination with iron, perhaps as the "*ferritin*" or "apoferritin" of V. Laufberger, 1937. Feeding with ferrous iron greatly increases the ferritin content of the intestinal mucosa of guinea pigs, and this disappears slowly (S. Granick, 1946).

Ferritin is described as containing up to 23 per cent of iron in protein combination. This is formed in the cells of the intestinal epithelium when their store of ferrous iron is depleted by lowering of the ferrous level of the plasma. Ferric iron is reduced in the body to ferrous, probably by SH groups, ascorbic acid, and perhaps other reducing components of the food (review, S. Garnick, 1946).

About twelve hours are required to remove a single dose of ferrous sulfate or of ferric chloride from the digestive tract, by absorption or evacuation (Austoni and Greenberg, 1940). The peak of the absorption occurs four to eight hours after feeding, when the food is largely in the small intestines; twenty-four hours after the last feeding practically all the unabsorbed isotope has passed into the colon, from which there is practically no absorption (Whipple *et al.*, 1938; P. F. Hahn *et al.*, 1938, 1939). Even under the best conditions, only about a third of the iron is absorbed. Iron absorption in healthy school children is greater than in adults, averaging about 13.5 per cent of radioactive iron (W. J. Darby, Hahn *et al.*, 1946). Diversion of the *bile* from the intestines does not lower the absorption of medicinal iron (P. W. Smith and Crandall, 1942), contrary to earlier reports.

The *quantity of iron in the feces* normally approximates that in the food (Kletzinsky, 1854), indicating either that the absorption is small or that the excretion occurs largely by the feces and balances the absorption. The latter holds true, for the feces contain this metal even in starvation; and when iron is injected subcutaneously, much more is excreted by the feces than by the urine. *Fistula experiments* have been more informative: A fistula in the lower ileum would separate the place of the principal absorption, the small intestine, from the principal excretion, the large intestine. Honigmann, 1896, found in this way that about 80 per cent of citrated iron was absorbed in the small intestine. Rabe, 1912, by using fistula dogs, found that the greatest absorption of saccharated iron occurs in the duodenum, the lower portions playing a progressively smaller role.

Experiments with radioactive iron show active absorption from gastric, duodenal and jejunal pouches (Hahn, Ross *et al.*, 1943).

Gastric absorption of iron has been confirmed by artificial stenosis of the pylorus with a rubber bag (Vahlquist *et al.*, 1945).

Microchemic evidence of the course of absorption is obtained by applying the color reactions of iron directly to the tissues. The macroscopic examination of the depth of stain gives a general idea of the quantitative distribution of the iron, the details being revealed by microscopic study. Since the iron compounds are likely to dissolve in the fixing solutions, many of the earlier experiments gave fallacious results. With improved technic, Macallum, 1894, Quincke and Hochhaus, 1896, and Abderhalden, 1906, found the reaction after the administration of iron preparations especially strong in the epithelial cells of the *duodenum.* The results below the duodenum were inconstant, depending upon the quantity administered. The *gastric epithelium* gives no reaction. The *large intestines* show diffused iron reaction of the epithelium and granules in the submucous leukocytes. It was generally assumed that this iron is in the course of excretion. However, Tartakowsky found that the large intestine shows no sulfide reaction in starvation or with iron-poor food, although the chemic examination of the intestinal contents proves the continued excretion of fixed iron. It would therefore seem that the excreted iron is too firmly combined to give the sulfide reaction, and that the sulfide reaction of the large intestine is also due to iron in the course of absorption. However, the amount absorbed here must be small. The absorption of iron must therefore take place mainly *through the cells of the duodenum.* This differs from other metals, which are absorbed *between* the cells (Hoeber, 1907).

Forms of Iron in Their Relation to Absorption.—The conceptions of these have undergone considerable modification. The "heme" iron of hemoglobin and cytochrome are the only forms of biological and medical interest which are now classed as containing "*organic iron,*" as an integral part of the molecule. Hemoglobin occurs only in blood and red meat. Cytochrome occurs in all aerobic cells (Keilin, 1928), but its quantity is relatively small. The iron of foods is therefore mostly "inorganic." "*Inorganic*" *preparations* contain ionizable iron, which either gives the ordinary iron reactions (with ammonium sulfide, ferrocyanide and hematoxylin) directly, or after treatment with dilute acid which renders it soluble (elementary iron and carbonate) or which breaks it loose from somewhat more complex ions. These complexes of "*masked iron*" are of all degrees of firmness, from the "double salts," such as iron and ammonium citrate, which are decomposed by weak acids, to the ferrocyanides, which require rather violent treatment. The *reserve iron,* which is stored in the tissues and constitutes much of the iron foods, is fairly firmly bound, and was formerly classed as "*organic.*" The iron of egg yolk, at one time considered typically "organic," is now classed as entirely "inorganic" (Tompsett, 1934), although its iron is firmly bound (M. C. Sherman *et al.*, 1934). In bakery yeast at least half of the iron is inorganic; about a third exists as heme compounds (Elvehjem, 1931).

The *iron content of foods* varies considerably. Blood, meat, yolk of eggs, and the green portions of vegetables, carrots, fruits, and so on, are especially rich in iron (17 to 40 mg. per 100 Gm. of dry substance); egg white, milk and the cereals (especially white flour) are poor in iron. Whole wheat, potatoes and the legumes are intermediate. Further data may be found in W. H. Peterson and Elvehjem, 1928. The *proportion of ionizable iron* is especially high (80 to 100 per cent) in fish, roots, tubers, cereals and legumes; high (above 50 per cent) in sweetbreads, fruits and green vegetables; intermediate in pork (15 to 47 per cent), and low in beef and mutton (10 to 25 per cent); (Shackleton and McCance, 1936; dipyridyl test). Wheat contains 3 to 5 mg. of Fe per 100 Gm., 18 per cent of this as fully available "inorganic" forms, equal in the treatment of anemic rats to the same amount of iron as ferric chloride (A. H. Free and Bing, 1940).

Simple ferrous and ferric salts differ in degree of absorbability, because ferric salts form insoluble compounds with proteins, phosphates and carbonates, even in the acid medium of the stomach and duodenum, while ferrous salts precipitate only when the reaction becomes alkaline (Starkenstein, 1928). Smaller doses of ferrous salts therefore suffice for nutrition and hemoglobin formation, but if enough ferric iron is taken, the needs are met just as completely, both in normal and in anemic subjects (F. Reimann and Fritsch, 1930; Lucas and Summerfeldt, 1939), perhaps because a sufficient amount of ferric iron is reduced to the ferrous state in the stomach and intestines (Starkenstein and Weden). The amount by which the dosage of ferric iron must be increased over that of ferrous varies according to the total iron income; from equality to as much as fifteen times clinically; with dogs there is little difference between ferrous and ferric (C. V. Moore *et al.*, 1944; Hahn, Lowe *et al.*, 1945).

Clinically, ferric salts gave much less rise of the serum iron concentration than did the ferrous, unless a reducing substance, such as ascorbic acid, was given (C. V. Moore *et al.*, 1939). In ligated loops of rabbits' intestines the absorption of ferric chloride was about a third that of ferrous chloride (O. Fürth and Scholl, 1936). Lintzel, 1933, found no absorption if the ferrous iron was rendered insoluble by the administration of alpha, alpha dipyridyl. It is conceivable, however, that ferric iron need not always be completely precipitated. In any case, in anemia the administration of adequate amounts of ferric iron results in the production of hemoglobin just as readily and completely as ferrous iron (Hahn, Bale *et al.*, 1938). Ferric ammonium citrate appears to be effective in some cases where iron-rich food is not so effective (Patek and Heath, 1936). The utilization of sodium iron phosphate by anemic rats is only half as efficient as that of ferric chloride (S. Freeman and Burrill, 1944).

Ferric ammonium citrate and analogous double salts have a somewhat special status, as they do not precipitate proteins directly; but they do so on acidulation, so that their utilization is practically the same as that of the ordinary ferric salts, and inferior to the ferrous (P. F. Hahn, Lowe *et al.*, 1945). *When the reaction is alkaline*, ferrous salts are also precipitated. The alkaline therapy of peptic ulcer interferes seriously with the utilization of iron and the regeneration of hemoglobin (Kellogg and Mettier, 1936).

Achlorhydria leads to a negative iron balance on moderate iron income (10 to 12 mg. daily); but large doses of ferric ammonium citrate are utilized as well as by normal subjects (Barer and Fowler, 1937). In experimental achylia, produced in dogs by extirpation of the gastric body and fundus, the absorption of iron from ferrous chloride is practically normal, and is only slightly augmented by administering hydrochloric acid (J. P. Quigley *et al.*, 1936).

The truly *organic compounds* of heme and cytochrome are not absorbed directly, but gastric juice and bacteria may break them down to inorganic. As this is generally incomplete, their utilization is imperfect (Elvehjem, Hart and Sherman, 1933), but even crystallized hemin may in this way be utilized up to 90 per cent when administered by mouth (Bing *et al.*, 1936). Up to 25 per cent of the iron of a liter of blood is absorbed from the human alimentary tract (D. A. K. Black and Powell, 1942).

The excretion of iron occurs mainly in the feces. The urine of man contains normally about 0.25 to 0.3 mg. per day, about a fiftieth of the amount in the feces. The latter is in large part unabsorbed iron, but considerable fecal excretion continues in fasting (Bidder and Schmidt, 1852; F. Mueller).

Mechanism of the Fecal Excretion.—The iron of the feces parallels their dry weight rather than their fluid (Reznikoff, 1932), indicating that it is excreted otherwise than by diffusion or filtration. It was at first assumed that the excretion occurred mainly by the *bile*, which always contains iron, but actual observation showed that the quantity of iron in the bile is small (mean, about 40 mg. per liter); and that it is not materially increased by the administration of iron (E. W. Hamburger, 1880; Anselm, 1892, 1916). A human biliary fistula yielded a maximum of 0.5 mg. per day, and this was not increased by intravenous injection of iron lactate (Henriquez and Roland). The biliary excretion of iron in normal dogs is constant at about 0.2 mg. per day. The bile also excreted little intravenously injected radioactive iron gluconate, unless there was blood destruction, as by acetyl-phenylhydrazine, but even then only 3 per cent of its iron is excreted by the bile, while the pigmentary radical is excreted in toto by this channel (W. B. Hawkins and Hahn, 1944). The main part of the iron must therefore be excreted directly into the intestines. This is confirmed by fistula experiments in which the access of food to the isolated parts of the intestines is prevented. Contrary to the older observers (Gottlieb, 1891; Honigmann, 1896), the small intestines appear to furnish the larger part of the excretion; the colon only about a fiftieth in dogs (Nicolaysen, 1935); very little in man (C. S. Welch *et al.*, 1936). In rabbits, after hypodermic and peritoneal injection of iron salts or hemoglobin, the main excretion is through the epithelium of the upper duodenum (Chevallier, 1914). The excreted iron is firmly bound, so that it gives the iron reactions only after incineration (Tartakowsky), in contrast to the black color of iron sulfide when inorganic iron is administered.

The *urine* always contains small quantities of iron, in man 0.003 to 0.8 mg. per day, median about 0.25 mg., with daily variations of about 50 per cent. Its concentration is perhaps a twentieth of that of the plasma (Hanzal and Bing, 1934; Tompsett, 1934; Henriquez and Roland, 1928; Dominici, 1929). The nature of the compounds has not been determined, but a part is loosely and a part firmly bound, and a part is removed by filtration through asbestos, indicating that it is in the formed elements (Hanzal and Bing). There is practically no increase if iron is administered by mouth (Marlow and Taylor, 1934), even for weeks (Gottlieb, 1890). Some increase occurs on intravenous injection of iron lactate in dogs (Henriquez and Roland); or iron and ammonium citrate in man (Lanyar *et al.*, 1933). Older investigators reported it somewhat increased in fever, nephritis, hepatic disease, leukemia and especially in diabetes (Tartakowsky, 1904), but Lanyar *et al.* found no increase in these and the other diseases studied, including polycythemia vera, pernicious anemia and hemolytic icterus. Iron is seen microscopically in the kidneys only if absorbable iron is administered or injected; not with a normal diet, nor with blood destruction.

Iron injected hypodermically or intravenously is largely *retained* over long periods, as reserve iron or as hemoglobin, so that there may appear to be no added excretion by the feces, and little by the urine (Nicolaysen, 1935; McCance and Widdowson, 1938). With parenteral administration of neutral radioactive ferric citrate to normal rats, less than 2 per cent was excreted in the urine and feces in the first four days (D. H. Copp and Greenberg, 1945). By the end of several weeks, however, most of the iron has been excreted by the feces (Gottlieb, 1891). With intravenous injection of *radioactive ferrous gluconate* into dogs, there is an initial extra output of 2 to 8 per cent of the injected iron, by urine and feces; then the excretion drops promptly to traces (P. F. Hahn *et al.*, 1939). If large quantities of iron and ammonium citrate or other iron salts are injected by vein, the excretion of iron by the bile and urine is promptly increased, in both cases as colloidal compounds. The *biliary excretion* is associated chiefly with the stellate cells and is decreased by blocking the reticulo-endothelial cells with India ink and by other forms of liver injury which have no effect on the biliary excretion of normal iron (Iwai, 1930). In the *kidneys*, the iron can be demonstrated by the ferrocyanide reaction to be excreted by the convoluted tubules, and none by the glomeruli, the colloidal state precluding filtration. If the injections are frequently repeated, the epithelium is injured (E. J. Stieglitz, 1921).

Normal Iron Retention, Distribution and Storage.—A positive iron balance is needed in growth, including pregnancy, and after loss of blood, for the formation of hemoglobin and cytochrome. If the income (deducting excretion) exceeds these needs, the retained iron is distributed among the organs and tissues, about as are other metals; but it is taken up more actively by the bone marrow, blood and muscle, especially with anemic patients (Austoni and Greenberg, 1940). Its microchemical reactions make it relatively easy to trace; and a considerable part is found in rather loosely bound form ("ferratin") as granules in the cells of the hematopoietic organs, in the liver and red marrow, and particularly in the spleen, to a less extent in the kidneys. In this form it remains until it is used or excreted. This constitutes an important *reserve stock* of iron which is drawn upon in hemorrhage, but which is conserved even when there is already a marked excess. It is regulated by the amount absorbed, rather than by excretion (P. F. Hahn *et al.*, 1939). The amount in the human liver and kidneys shows a characteristic life curve (Brückmann and Zondek, 1939).

The *iron content of the entire blood* averages 50.1 mg. per 100 cc. for men; 43.4 mg. for women; 44 mg. for children (A. Sachs *et al.*, 1935; Sobel and Drekter, 1933); but nearly all of this is hemoglobin. However, 5 to 10 per cent of the iron of the erythrocytes is in easily detachable ionized and dialyzable form (Lintzel, 1925), intermediate in the transformation of hemoglobin into bile pigment. The *plasma iron*, in man, ranges between 0.06 and 0.7 mg. per 100 cc. (Fourweather, 1934; Tompsett, 1934, Marlow and Taylor, 1934). The variations are due at least in part to the absorption of ingested iron: In dogs, Bing, Hanzal and Myers, 1935, found the serum level 0.1 to 0.2 mg. per 100 cc. in fasting (entirely inorganic). After oral administration of iron chloride or reduced iron, it rose to a peak of 0.3 to 0.55 mg. in three or four hours, returning slowly to the fasting level in twelve to twenty-four hours. Patients with pernicious anemia and acutely ill patients do not show the rise of plasma iron on oral administration regardless of the state of their iron reserve (C. V. Moore *et al.*, 1939). Radioactive iron, administered by mouth to anemic dogs, is transported in the *nonprotein portion* of the plasma (Hahn *et al.*, 1939).

Variations of Reserve Stock.—This disappears ("*asiderosis*" of Quincke) gradually when a diet poor in iron is given, or when there is an extraordinary use of iron, as after hemorrhages or during pregnancy (when considerable iron is transferred to the fetus). In acute hemolytic anemia of rabbits, the reserve iron largely disappears, especially from the liver cells, when the blood is regenerated. Small amounts are still present in the endothelium of the hepatic capillaries, in the spleen and in the renal cortex (Muir and Dunn, 1915). The deposits increase, on the other hand, when the iron of the food is increased or when blood is destroyed, as in toxic and pernicious anemia. The chemical nature of the tissue and storage iron is not clear; 15 to 70 per cent is nonhematin, probably in a variety of forms, presumably ferric, which may be mobilized at different rates. The most anemic animals contain considerable nonhematin iron in the liver and spleen and especially in the heart and skeletal muscles. Myohemoglobin also is not diminished in anemia (review, M. O. Schultze, 1940).

Data on the *iron content of different tissues* of dogs and rabbits are given by Elvehjem and Peterson, 1927. The *liver* is normally rich in iron (this is true likewise of animals which do not form hemoglobin—molluscs, crayfish, lobster, and so forth). The liver iron decreases with iron-poor food, or when there are extra demands for iron, as in pregnancy or after hemorrhage. The iron content of the liver may thus be taken as an index of the iron stock of the body. By prolonged high iron income (for three to four years), the liver iron of rabbits may be raised to 100 or 200 times the normal (from 0.036 per cent of the dry weight to 3.4–7.7 per cent), without hemochromatosis or other evidence of damage to the liver or pancreas (Polson, 1933). *Hemochromatosis* represents a partial accumulation of iron-containing pigment granules, chiefly hemosiderin (Rous *et al.*), associated with fibrosis, in the parenchyma cells or connective tissue, especially in the liver, which may contain 38 Gm. of iron, ten times the normal iron content of the entire body, including the hemoglobin. The formation of a blue wheal on intradermal injection of faintly acidulated 0.5 per cent potassium ferrocyanide has been proposed as a clinical test of hemochromatosis (H. R. Fishback, 1938). The *spleen* is an important depot of reserve iron, as granules of loosely bound iron. The quantity varies with the iron income and blood destruction (Chevallier, 1914). Its reserve affinity surpasses that of the liver, for animals fed from birth on iron-free food, whose liver is free from reserve iron, contain some in the spleen

(Schmidt, 1912). With normal iron metabolism, the spleen is not essential, and its excision does not entail any constant or important changes in iron balance; probably not even when the iron income is inadequate (E. Lauda and Haam, 1928). With hemolytic poisons, however, excision of the spleen affects the formation of hemoglobin (G. B. Ray and Isaac, 1930). Relatively large stores of iron and copper may accumulate in the liver and spleen during chronic secondary anemia (M. Sandberg *et al.*, 1942).

In experimental anemia, induced in dogs by repeated hemorrhages, the iron store of all organs can be largely exhausted in two or three months. When iron is administered orally to such animals, it is converted into hemoglobin, at first with little storage in the liver; more prolonged administration gives slight and variable storage (P. H. Hahn and Whipple, 1936). Tracing with radioactive iron indicates that the storage under these conditions is much greater in the liver than in the spleen (Hahn *et al.*, 1938). A *sex relation* of iron storage has been demonstrated in rats, females accumulating a larger store at sex maturity than do males. During pregnancy the store is depleted, and after parturition it is again built up rapidly to its former level. This storage is destroyed by castration and restored by injection of follicular hormone. The cycle provides for the *iron supply of the fetus*, whose store at birth is in direct relation to the amount stored by the mother (Steenbock *et al.*, 1936). When a single dose of radioactive iron is fed to the mother near the end of gestation, it appears in the fetal circulation within forty minutes. It is widely disseminated in the fetal tissues, with the highest concentration in the erythrocytes and the largest quantity in the liver (W. T. Pommerenke, Hahn *et al.*, 1942). The liver store of iron in newborn infants of normal mothers averages 50 mg. Their hemoglobin concentration is high, averaging 22 per cent; their blood volume is also high, 15 per cent of body weight. The destruction of the excess hemoglobin begins almost immediately after birth, and is completed in nine to twelve weeks, at 12.5 per cent (G. Stearns, 1939).

Intravenously injected iron compounds leave the blood stream practically completely within two or three hours. At this time, only 10 per cent has passed into the excreta; about 50 per cent is deposited in the liver, and the remainder in other organs, spleen, kidney, intestines. Hahn and Whipple, 1936, found 50 to 77 per cent in the liver and spleen, the liver having a much larger share than the spleen in this temporary storage (D. H. Copp and Greenberg, 1945). In *anemia*, parenterally administered iron is transformed almost completely into hemoglobin (Hahn and Whipple, 1938). With ***intravenous injection of 10 to 25 mg. of radioactive ferrous ascorbate into normal individuals***, 70 per cent is converted into hemoglobin in ten days, 100 per cent in ten weeks. In *hypochromic anemia* the utilization is more rapid, 100 per cent by the ninth day. In *hypoplastic anemia* only 1 to 1.5 per cent is utilized. In *pernicious anemia* in relapse the conversion amounts to about 30 per cent in nine days and remains at this level until liver therapy is started, when it rises to 100 per cent. Various types of hemolytic anemia give a total utilization of 14 to 16 per cent, reached in six to nine days (R. Dubach *et al.*, 1946). In experimental *tuberculosis* of rabbits, the tubercles accumulate iron from intravenous injection of ferric chloride (Menkin, 1934). *Intravenously injected colloidal iron* ("dialyzed iron") is at once precipitated in the blood, forming emboli in the lungs, and considerable accumulations in the liver and spleen, chiefly in the endothelial cells. In time, the iron passes from the lung to the spleen and thence to the liver, where it is retained for long periods (fourteen months). From the liver it goes gradually into the lymph gland, where there is further prolonged retention. Eventually a part is excreted by the kidneys and cecum (Polson, 1929; Cappell, 1930).

Fate of Hemoglobin.—If free hemoglobin occurs in the plasma, in concentrations above 0.12 per cent as a result of its injection or of extensive hemolysis, the excess is mainly filtered through the kidneys, producing hemoglobinuria (Pearce, Austin and Eisenbrey, 1912). On standing, the urinary hemoglobin changes fairly rapidly to methemoglobin (Drabkin *et al.*, 1935). With intravenous injection of dissolved hemoglobin into normal man, it does not appear in the urine until its plasma level exceeds about 100 mg. per 100 cc. With injections up to 16.4 Gm., less than 15 per cent goes into the urine. In patients with preexisting albuminuria, traces of hemoglobin may pass into the urine when the plasma level is 40 mg. per cent. The plasma bilirubin increases parallel to the injected hemoglobin (D. R. Gilligan *et al.*, 1941). A part of the free hemoglobin of the plasma is decomposed into bile pigment, or all if the concentration is lower, and therefore with the normal destruction of the corpuscles. In this decomposition, the iron is split off and deposited as storage iron, so that injection of hemoglobin increases markedly the iron content of the liver, spleen and bone marrow. With hemolysis so severe as to destroy nearly half of the blood in three days, almost all the iron of the destroyed corpuscles was found deposited in the liver, spleen and kidneys; a third of the total iron of the blood may be thus deposited in twenty-four hours (Muir and Dunn, 1915). The iron liberated by the normal destruction of the corpuscles may be utilized again for forming new corpuscles, so that it is practically impossible to produce severe anemia in adult animals by limiting the iron of their food. However, a part of the liberated iron is lost by the feces and urine.

Re-Use of Hemoglobin.—The lifespan of an erythrocyte, as judged by blood groupings of transfused blood-averages 129 days (S. T. Callender *et al.*, 1945); 0.75 per cent of the hemoglobin would therefore need to be regenerated daily, corresponding to nearly 20 mg. of iron. As the daily income may be only a third of this, at least two-thirds of the hemoglobin iron must be used again for this purpose. The labeled iron of hemoglobin liberated by age, trauma, or toxic hydrolysis is almost immediately and quantitatively utilized for new erythrocytes, even when there is abundant store of reserve iron (P. F. Hahn, Bale and Balfour, 1942).

Products of Hemoglobin Destruction.—In the decomposition of the liberated hemoglobin, the hematin is split into hemosiderin, which carries the iron, and into an iron-free fraction, presumably hematoporphyrin, which in turn is converted into bilirubin, and this into the fecal and urinary pigments, stercobilin and urobilin. In trauma, a transitional degeneration product with "masked" iron is taken up promptly by the mesenchymal and epithelial cells (N. W. Popoff and Popoff, 1943). With injection of hemoglobin or extensive hemolysis, the bilirubin formation may exceed the excretory capacity of the liver and lead to icterus (Pearce *et al.*, 1912).

Urobilinogen is also increased in pernicious anemia, and when polycythemia is treated with phenylhydrazine. With feeding of blood, the absorption is so limited that it does not modify the bile flow or the secretion of bile pigments (Whipple and Hooper, 1917). The destruction of the hemoglobin and the formation of bile pigment is *accomplished by the reticulo-endothelial cells*, in all organs where these are found, in the spleen, liver, bone marrow, lymph nodes, and so forth. The share of the liver in the bile pigment formation is probably smaller than that of the spleen (Whipple and Hooper, 1913; F. C. Mann). The decomposition of hemoglobin and formation of bile pigments is effected even by tissue cultures of histiocytes (Rich, 1924). Analogous changes are observed when blood is extravasated into the tissues. The scavenger function of the reticulo-endothelial system begins with the phagocytosis of the fragmenting erythrocytes, which break down throughout the vascular system when their life span is run, averaging four months in dogs (Hawkins and Whipple, 1938) and estimated at one-half to two months for man. The spleen is especially prominent in the disposal of the aged corpuscles, probably retaining them in the sluggish current through its network, and perhaps mashing them in its rhythmical contractions; but if it is excised, other reticula, especially the bone marrow, fulfill its hemoclastic functions, without any marked disturbance. In normal animals, splenectomy, with or without hemoglobin injection, does not modify bile pigment excretion (Hooper and Whipple, 1917).

Spleen as a Colloid Trap.—The colander function of the spleen is exerted not only against the blood corpuscles, but also against other particles in the blood, including suspension colloids. In this process the reticulo-endothelial system is concerned, probably partly by adhesiveness and partly by engulfing the particles.

Chemical Structure of Hemoglobin.—Hemoglobin makes up about a third of the mass of the erythrocytes. It consists of a protein, *globin*, probably allied to histone, which differs in different animals, combined with about 4 per cent of hematin (hemochromogen), which in turn contains 8.5 per cent of iron, so that hemoglobin contains 0.37 per cent of iron, as four ferrous atoms to the molecule. The chromogen or heme is probably identical in different animals. It is a compound of ferrous iron with a porphyrin molecule. *Porphyrin* is a complicated ring formed by the linkage of four methyl pyrrhole rings. In forming the heme, the four nitrogens of the porphyrin unite with the six places of iron, analogous to ferro- and ferricyanide, $K_4Fe(CN)_6$ and $K_3Fe(CN)_6$. This leaves two places in the Fe free which may be filled on the one hand with globin, nicotine, pyridine, and so on, and on the other hand with oxygen, carbon monoxide, cyanide, and so forth. Many iron porphyrin compounds are found in all cells and tissues and constitute a family of *hemin compounds*, viz., the various forms of *cytochrome* found by Keilin; and Warburg's respiration ferment (L. Michaelis, 1931).

Muscle hemoglobin, which occurs in certain muscles, represents about a fourth of the total hemoglobin of the body. It differs from blood hemoglobin in that its molecule contains only one iron atom, and by a high affinity for oxygen and relatively low affinity for carbon monoxide. It furnishes muscle with a limited local oxygen store. Its quantity is greater in the muscles that require sustained repetitive activity of considerable force, such as the heart muscles of larger animals and the pectoral muscles of birds. Its concentration increases with age and activity (G. A. Millikan, review, 1939).

Oxygenation and Oxidation.—Hemoglobin can be oxidized in two divergent ways: (1) It combines reversibly with molecular oxygen without the iron being oxidized from ferrous to ferric. This is *oxygenation.* (2) Ferrous may be oxidized to ferric iron, by *true oxidation;* the oxidized hemoglobin is methemoglobin. True oxidation to ferric does not occur perceptibly with molecular oxygen, but only by an oxidant, *i. e.*, hemoglobin is not auto-oxidizable. This is essential to its function as an oxygen carrier. Most *other heme compounds* in the ferrous state are auto-oxidizable to ferric and therefore act as oxygen catalysts or as oxidants of organic foodstuffs, *i. e.*, as respiratory ferments. The majority of organisms require some iron, even those which do not form hemoglobin. (The blood of some *invertebrate animals* contains copper or manganese in place of iron.) The *effects of iron and copper on yeast growth* are similar to their effects on hemoglobin formation, suggesting the analogy of the hemes and the cytochromes (Elvehjem, 1931).

Ferric Salts as Catalysts.—The oxidation of glucose by hydrogen peroxide occurs slowly *per se;* by the addition of 0.001 per cent of ferric sulfate the oxidation occurs much more rapidly, so that the mixture may boil (quoted from J. Stieglitz, 1924). The catalytic effect is produced only by ferric ions.

The *activity of vegetable peroxidases* appears to increase with the iron content up to a certain point; but by further purification the activity increased as the iron content fell; so that iron is not a constituent part of the enzyme, but only an accelerator (Willstaetter, 1927).

Hematoporphyrin occurs in small amount in normal blood and urine and may be greatly increased in a variety of diseases, and especially in poisoning by sulfonal and barbital, so as to give a burgundy color to the urine. Smaller amounts appear in lead poisoning. Its occurrence in these conditions is capricious (review, V. R. Mason *et al.*, 1933). It causes marked hypersensitiveness of the skin to light. After hypodermic injection and exposure to light, mice die in a few minutes to several days according to the dose (Hausmann, 1910; Hutschenreuter, 1933; review, K. Dobriner and Rhoads, 1940).

Since the animals show increased motor activity, hematoporphyrin hydrochloride was introduced clinically as "Photodyn," against *psychotic depression* (Huhnerfeldt, 1931) with apparent improvement in about half the cases (Angus, 1936); but multiple neuritis has been reported (Thornes, 1937). Its injection into animals causes marked degeneration in the nerve cells, myelin sheath and axis cylinders of the spinal cord, in peripheral nerves and in sympathetic ganglia. In the presence of oxygen and light, visible and ultraviolet, hematoporphyrin develops proteolytic properties, hydrolyzing fibrinogen and other proteins, including serum albumin (Howell, 1921; M. J. Boyd, 1933). Injected into rabbits, it produces significant changes in the quantity and composition of the urine, indicating increased breakdown of nitrogenous and non-nitrogenous metabolites and increased Cl excretion (Hinsberg and Merten, 1938). It also seems to have some relation to the growth of the bone (Borst, 1930).

Fate.—Intravenously injected hematoporphyrin leaves the blood stream rapidly, and is scarcely measurable after twenty-four hours. It is largely taken up by the liver and eliminated by the bile, sometimes partly by the urine. After hypodermic or intraperitoneal injection, it appears promptly in the blood, increasing slowly to a maximum in twelve to twenty-four hours (Smetana, 1938). It is apparently not absorbed from the oral administration (Hutschenreuter, 1933).

Chlorophyl, the characteristic green pigment of plants, essential to their peculiar metabolism and synthetic functions, is formed on the same four pyrrhole ring pattern as hemochromogen, but united to magnesium instead of iron. Two closely related chlorophyls, a and b, have been isolated pure by Willstaetter, and there are doubtless others. They constitute 0.1 to 0.2 per cent of the fresh green leaves. The structural similarity suggested that the ingestion of chlorophyl would promote the formation of hemoglobin in anemia, but this is not so (Whipple and Robscheit-Robbins, 1925; Patek, 1936). The greater part of the ingested chlorophyl is eliminated as pheophytin in the feces (F. T. Edwards and Holley, 1932). The special value of green vegetables is due to their carotene and other vitamins.

Parenteral injection of chlorophyl may produce fatal hemolytic anemia in mice and rabbits if these are exposed to light, red and yellow being especially effective for this photodynamic action (Guerrini, 1933). Direct stimulant effects of chlorophyl on *excised heart, intestine and uterus* have been reported (Gordonoff, 1927; other pharmacologic effects, Rentz, 1929).

Local application of a *water-soluble chlorophyl* derivative is claimed to hasten the healing of wounds (L. W. Smith and Livingston, 1943) and ulcers (E. Gahan *et al.*, 1943), but requires further confirmation. It is reported to be bacteriostatic by interfering with oxidation-reduction. Intravenous injection is not toxic (L. W. Smith, 1944).

The formation of hemoglobin appears to occur by the transformation of the iron-containing nuclear chromatin of the hematoblasts (A. B. Macallum, 1920). Protoporphyrin is probably a step in its synthesis. The hemoglobin then passes from the nucleus into the cytoplasm (Villa, 1930), and in the mammalian corpuscles the nucleus disappears into the cytoplastic reticulum (Macallum, 1931). The erythrocytes themselves are derived from the reticulo-endothelial cells that line the blood sinuses; in early embryonal life quite diffusely, later largely in the spleen and liver, and at birth almost exclusively in the red bone marrow, although the spleen and liver remain potential dormant centers throughout life (review, H. E. Jordan, 1942). Red bone marrow replaces fatty marrow during hematopoietic stimulation. It is a stagnant area in which erythrocytes are formed and matured through long periods. The small endothelial cells develop successively through megaloblasts (colorless, nucleated basophilic cells), erythroblasts (progressively less basophilic), normoblasts (acquiring hemoglobin) and reticulocytes (disappearance of nuclei which mature rapidly into the erythrocyte when it enters the circulation) (review, M. O. Schultze, 1940; Middleton and Meyer, 1935). Notwithstanding this elaborate course, radioactive iron appears in the erythrocytes of anemic dogs in a few hours after its oral administration (Hahn *et al.*, 1939).

The *regulation of hemoglobin and red cell production* to maintain the normal level is ordinarily very efficient. The hemoglobin concentration of normal human blood is practically independent of race and habitat, except for altitude and nutritional state. It averages 15.8 Gm. (14.5 to 18.5) per 100 cc. in men, 13.8 (12.5 to 15) in women, 12.0 in children (V. C. Myers and Eddy, 1939). The mechanism of the regulation is not known, but it extends back as far as the absorption of iron, which is much greater when there is need for additional blood formation. The most potent measure for increasing hemoglobin and erythrocyte production is the need for them, as after hemorrhage, and the rate of hemoglobin production increases with the degree of the deficiency, being one and a half times as high when the hemoglobin level is 6 per cent than when it is 11 per cent (F. S. Robscheit-Robbins and Whipple, 1941). Oxygen deficiency as in mountain sickness sets them to a higher level. Injection of hemolyzed blood is also a potent stimulus (review, S. Isaac, 1920). The administration of iron, copper and other metals facilitates restoration of the normal level, and cobalt produces polycythemia. Hematopoiesis is also stimulated by parenteral injection of extracts of spleen (Krumbhaar and Musser, 1914), of bone marrow, and more potently by both together (Leake, 1923). All these agencies cause hyperplasia of the bone marrow. The production of red cells is decreased, with resulting anemia, when the red marrow is injured, as by toxic doses of the metals, or by benzene and some of its derivatives. Temporary increase of the red corpuscle count, by as much as 250,000, may result from contraction of the spleen.

In blood donors, with the removal of 555 cc. of blood the hemoglobin dropped acutely from an average of 12.8 to 10.3 Gm., per 100 cc., a loss of 2.3 Gm. per 100 cc. or 18 per cent. It required about fifty days to replace the loss, the hemoglobin being reformed at the average daily rate of 0.05 Gm. per 100 cc. for men; 0.04 for women. Oral administration of iron ammonium citrate, 1 Gm. per day, increased the daily hemoglobin regeneration by half, shortening the average restoration period to thirty-two days. Repeated donations slow the recovery and diminish the response to iron administration (W. M. Fowler and Barer, 1942).

Auxiliary Action of Copper and Other Metals in Blood Formation.—The utilization of suboptimal amounts of iron for the formation of hemoglobin is promoted by the oral injection of minute quantities of copper (0.16 mg. per day for rats), which stimulate the bone marrow (E. B. Hart *et al.*, 1927; C. A. Elvehjem, Hart and Kemmerer, 1929; D. W. Frost *et al.*, 1940). The absorption and retention of iron does not appear to be promoted by the copper (Josephs, 1932), but only the formation of erythrocytes and hemoglobin, and when this is efficient as in hemorrhage (Whipple *et al.*), or with a liberal iron income, the copper seems to be superfluous. This may account for the discrepant conclusions of different workers as to the need of copper, even when similar conditions were sought (Bing, Sauerwein and Myers, 1934). The effects of copper may also be produced by a large number of other metals (Ni, Ge, Mn, As, Ti, Zn, Ru, Cr, Va, Se, Hg). All these, as well as iron itself, hasten the mobilization of reticulocytes from the bone marrow. They may produce polycythemia in normal animals, but excessive dosage, at least of some of the metals, may injure the bone marrow and may therefore fail to improve anemia, or they may even exaggerate it (review, M. O. Schultze, 1940). This may account for some of the discordant experimental results. Clinically, this has been known especially for lead, and also for arsenic and mercury.

Therapeutic Insignificance of Copper in Anemia.—The optimal dosage of copper is so small that extreme precautions must be taken to exclude it from the food and iron, in order to demonstrate its effects. The artificial addition of copper to ordinary foods or iron preparations is therefore generally superfluous. However, it is reported that hemoglobin regeneration in anemic infants is improved by adding copper to the iron therapy in the ratio of Cu 1: Fe 25. The iron, copper and manganese content of common foods is reviewed by M. A. Hodges and Peterson, 1931, in J. Am. Diet. Assoc., *7:* 6. The *average daily intake* for man would approximate: iron, 15.44 mg.; manganese, 2.39 mg.; copper, 2.26 mg. The occurrence of these metals, and also of aluminum and zinc in foods, and their role in nutrition are also reviewed by M. S. Rose, 1929, in J. Nutrit., *1:* 541.

The addition of a mixture of arsenic, manganese and iron increases the hemoglobin synthesis of rats on a restricted diet, more than does a mixture of iron with either arsenic or manganese alone (J. T. Skinner and McHargue, 1946).

Iron Therapy in Anemias.—Interest in iron therapy was revived by the chemical demonstration of iron in the blood by Menghinis, 1746, and his claim that this could be increased by a diet rich in iron. Foedisch, 1832, demonstrated that the blood of chlorotic patients is low in iron; and Andral, Gavaret and Delafond, 1842, claimed that the administration of iron to chlorotic patients increases the number of red cells. It was assumed that it was essentially an inorganic food element, and that it would be useful in all conditions characterized by low hemoglobin. This generalization was not borne out by practical trial. It proved notably ineffective in anemias in which there is no iron deficiency; especially in pernicious anemia and many acute anemias, *f. i.*, that of hemorrhage, where recovery is probably as rapid without iron medication, owing to drawing on the iron stores of the body.

The *reticulocyte response as index of iron therapy* has the advantage of giving definite, prompt and quantitative data. It is not so regular or so extensive as the response of pernicious anemia to liver. A positive reticulocyte response of varying degree to iron therapy has been observed in the anemias of chronic blood loss, dietary defects, gastro-intestinal disorders, pregnancy, ill defined anemias and chronic microcytic anemias with achlorhydria, although the response is not so regular nor so extensive as that of pernicious anemia to liver. The degree of response increases with the degree of anemia, as with liver therapy in pernicious anemia; but the relation is not constant, following the hemoglobin more closely than the blood count. Infections and other complications hinder the response. Patients with achlorhydria respond less to iron than those with normal acidity. In all cases, large doses of iron are much more effective than small doses (Minot and Castle, 1931; Minot and Heath, 1931).

Nutritional Anemia in Growing Individuals.—Rapid growth requires relatively large quantities of iron for the increase of tissue and especially of blood, and anemia readily results if the iron income is inadequate. This is likely to be so in infants since milk, the chief food, is poor in iron. *Cows' milk* contains 0.4 to 0.7 mg., average 0.5 mg., per liter. It is not influenced by administering iron to the cow (Elvehjem, Herrin and Hart, 1927). The content of human milk ranges about five times higher, *i. e.*, average 2.5 mg. per liter (Dorlencourt and Calugareanu-Nandris, 1926). The newborn are protected for a time by the large iron reserve which they have stored in fetal life. This suffices normally until the time when the young are naturally weaned; but the stock is exhausted in a few months, and if the infant is kept too long on a milk diet, infantile anemia sets in, especially with premature infants.

owing to their smaller iron storage and less developed bone marrow.

The *nutritional anemia of young rats* has been extensively studied as evidence of the utilization of inorganic iron and for demonstrating the effect of auxiliary metals. Young animals on a milk or milk and rice diet develop a progressive fall of hemoglobin percentage and become emaciated, with stunted growth. As soon as iron, in any form, is added to the diet, the animals recover rapidly and resume growth (Hoesslin, 1890; Cloetta; Tartakowsky; Abderhalden). It has been used as a test of the relative effectiveness of iron preparations; the differences among these appear quite unimportant (H. S. Mitchell, 1927).

Bunge found that the proportion of iron in newborn animals is high (increasing rapidly in the last three months of fetal life; Hugounencq, 1899), and that it decreases steadily during the period of lactation (because milk is poor in iron) until it has reached a practically constant quantity—about the seventeenth day in guinea pigs or rabbits, and the twenty-third or twenty-fourth day in dogs. Animals of the same litter can therefore be used for controls, some being fed, at the end of the lactation period, with iron-poor food, others with the same food to which the iron preparation is added. Rice and milk, which contain a small proportion of iron, are commonly employed. The animals which do not receive the iron remain small and emaciated. Those which receive iron, in any form, show an unmistakable increase in the total iron content of the body, especially of the liver, spleen and bone marrow (Hall, 1894; Kunkel, 1895; Oerum, 1906). The response to iron administration may be followed in living animals by the *reticulocyte count.* In the circulating blood of normal young rats, reticulocytes form about 3 per cent of the total red corpuscles. As milk anemia develops, the reticulocyte percentage increases in six days to 15 or 20 per cent. If iron is now added, there is a further increase to 30 or 40 per cent in six days, then a decrease to normal in three days or longer. The addition of copper or other metals hastens both phases of the process, so that a normal level is reached in six to eight days (H. H. Beard, Myers *et al.*, 1931). *Female rats* improve under iron and copper more rapidly than males (M. C. Smith and Otis, 1937); this is probably due to the larger intake of the restricted diet by the males (H. H. Mitchell and Hamilton, 1937).

Nutritional anemia in adults may result from long-continued injudicious diets. It is probably an element of hypochromic anemias, including chlorosis, although there are other factors. Bethell *et al.*, 1939, found that half of the pregnant women examined by them were anemic from inadequate iron income. In most cases this can be controlled or prevented by 0.3 Gm. of ferrous sulfate, three times daily, with a good diet (C. C. Sturgis, 1946).

The *anemia of pregnancy* disappears spontaneously within a week after parturition, if the diet during gestation was adequate in iron; otherwise it is more persistent. It responds to full doses of iron and ammonium citrate (6 m. per day), but not to small doses (0.5 Gm. per day) or to liver extract. The hemoglobin level of the fetus is not lowered by anemia of the mother (Strauss, 1932).

The oxygen affinity of the hemoglobin is lower in fetal than in maternal blood; but this is reversed if the corpuscles are suspended in saline solution (E. F. McCarthy, 1943).

Because of the iron reserve, nutritional anemia is not readily produced in relatively short-time experiments on adult animals, except by *complete fasting.* In this the body weight decreases and the blood volume diminishes in a fairly corresponding degree. The blood count also falls, however, especially in birds (Barlow, 1926), and to a less degree in rats (Whitehead). This is due in part to hydremia, but also to excess destruction of the corpuscles, perhaps by the bacteria which invade the blood from the intestinal tract. This anemia is not prevented by the administration of iron (Barlow, 1926). The anemia of rice disease is similar to that of starvation; it is counteracted by laxatives which diminish the bacteremia (Barlow; Whitehead).

Anemia of Acute Hemorrhage.—Every loss of blood necessarily results in temporary anemia; but after a single severe hemorrhage, healthy adult individuals recover their blood count and hemoglobin completely, after some weeks, even on an iron-free diet. The reserve iron therefore suffices for the restoration of all the hemoglobin lost in a single nonfatal hemorrhage (Kunkel, 1895; Tartakowsky, 1903; Williamson, 1924).

Even if the hemorrhage is rendered more severe, by repeating the hemorrhage of a fourth of the blood volume on two successive days, complete restoration of hemoglobin and corpuscles occurs in four to twenty weeks with dogs. It may be hastened by a mixed diet (four to seven weeks), and still more by a meat diet (two to four weeks), but not by the administration of medicinal iron. The accelerating effect of the diet is therefore not due to the iron, but to some other factor (Whipple, Hooper *et al.*, 1918). Liver is especially effective (Williamson, 1927).

Hemolysis Products on Blood Regeneration.—Blood regeneration is much more rapid after hemolytic poisoning than after simple hemorrhage. This has been attributed to stimulation of the bone marrow by substances liberated in the destruction of the corpuscles, presumably from their lipoid envelopes (Kepinow, 1910); and the injection of hemolyzed blood into bled animals leads to much more rapid recuperation than would correspond to its iron content (Itarri, 1911). The intramuscular injection of 10 to 20 cc. of human defibrinated blood was used in severe anemia (Weber, 1909), but its advisability is doubtful.

Chronic hemorrhage is a frequent cause of clinical secondary anemia, for it tends to exhaust the reserve iron faster than it can be replenished from the ordinary diet, which furnishes iron for not more than 30 cc. of blood daily, and probably less. It can be effectively corrected by the administration of iron, but more promptly if the diet also includes other hematogenous factors; meat, kidney and particularly liver (Whipple, 1938). *Chronic hemorrhage anemia induced experimentally in dogs* is an important means of testing the utilization of iron preparations and the efficiency of other measures. It was introduced for this purpose by Kunkel, 1895, and Tartakowsky, 1903, and developed and improved by Whipple and his associates, 1918 to date.

The reserve iron of dogs can be exhausted by this means in two or three months, and the hemoglobin may then be maintained for years at about half the normal level. The parenchyma (reserve) iron of such standardized depleted dogs is 1 to 2 mg. per 100 Gm. of fresh liver, kidney and pancreas, 5 to 6 mg. for spleen, 10 mg. for red marrow (Hahn and Whipple, 1936). If iron is injected *intravenously* into such dogs, it is converted quantitatively into additional hemoglobin, the full theoretical quantity of 3 Gm. of hemoglobin for 10 mg. of iron, practically regardless of dosage. The formation of additional hemoglobin is therefore a measure of the absorption of iron when given by mouth. This varies with the dose, 40 mg. per day being most efficient. With this optimum dosage, the absorption averages about 35 per cent of the ingested inorganic iron, the same for ferric, ferrous or reduced; 10 per cent for ingested hemoglobin iron (whole blood); 44 per cent for liver (Whipple and Robscheit-Robbins, 1936). The absorption of liver and other organ iron does not parallel the dipyridyl (ferrous) fraction (Hahn and Whipple, 1938). When radio-active iron is fed to anemic dogs, either as ferrous sulfate or as ferric chloride, it can be demonstrated in the erythrocytes within four hours, and within two or three days it is converted almost completely into hemoglobin; up to three-fourths of the total amount (4.1 to 12.7 mg.) absorbed is in the erythrocytes within eighty-four hours, presumably as hemoglobin. The percentile absorption is greater with small than with large doses. Dogs that were not anemic had absorbed little (0.08 to 0.24 mg.), but again a quarter to a half of this was in the erythrocytes (Hahn *et al.*, 1938, 1940).

The plasma proteins can also be kept at low levels, 4 to 5 Gm. per cent, by chronic hemorrhage with adequate iron but low protein intake; such animals are suitable for testing the restoration of plasma protein by various proteins and amino acids (F. S. Robscheit-Robbins, Miller and Whipple, 1943).

Toxic anemias may be caused by injury to the corpuscles, as with hemolytic poisons (saponin, cobra venom, hemolytic sera, hookworm infection, AsH_3, toluylene diamine), or by injury of the bone marrow (radium, benzene, aniline, nitrobenzene, trinitrotoluene, CCl_4, Pb, As, P, ricin); *chronic infections* (endometritis; nephritis) inhibit the absorption of iron and injure the bone marrow (Robscheit-Robbins and Whipple, 1936), so that the absorbed iron is not utilized (W. M. Balfour, Hahn *et al.*, 1942). Blood destruction stimulates the bone marrow at first, but this is injured if the stimulation is too great or too prolonged. Although part of the liberated iron is stored in the spleen and liver, considerable is lost by the feces (Fukui, 1926), and the hemolyzed hemoglobin by the urine, so that iron administration hastens recovery (hookworm, Rhoads and Castle, 1932; toluylenediamine, Petow *et al.*, 1930; infections, Minot and Heath, 1931), but they are useless unless the cause is removed. In *pernicious anemia*, iron therapy is a rather minor adjuvant of the liver treatment, since the destruction of the corpuscles (probably through an unknown hemolytic agent) is accompanied by a considerable increase of the reserve iron of the liver and spleen (Rumpf, 1901) and of the dissolved iron of the spleen (Erben, 1900). The urinary excretion of iron remains normal (Queckenstedt, 1913).

Iron in Chlorosis.—The "green sickness" is confined to girls in puberty, and disappears spontaneously at maturity. It is distinguished by hypochromemia, *i. e.*, marked decrease of hemoglobin, with little or no decrease of the corpuscle count. It appears to be an exaggeration of the normal tendency of adolescent girls toward anemia, created by their increased need for iron on account of growth, menstrual losses and perhaps other features of sexual development, with inadequate dietary income of iron. It is promptly and completely corrected by the medicinal administration of iron. The absorption of iron is normal. The maximum rate of hemoglobin regeneration under iron occurs usually between the second and fourth weeks of treatment (W. P. Murphy, 1933). It is indicated by the height of the reticulocyte response and by the rate of hemoglobin increase.

The disease appears to be less common than formerly, presumably because the regimen of girls has become more hygienic. However, 26 per cent of "healthy" student nurses have hemoglobin readings of 70 to 79 per cent (Patek and Heath, 1936). The tendency is exaggerated by the low iron income generally characteristic of most chlorotic subjects, as first pointed out by Stockman, 1895, who found that the diet of chlorotic girls in Scotland contained only 2.8 to 3.2 mg. of iron per day. Four chlorotic patients studied by Patek and Heath, 1936, in America averaged 5.4 mg., which is adequate for adults, but in the lower range. Twenty days of diet rich in iron raised their hemoglobin only from 30 per cent to 36 per cent; but it rose to 73 per cent in sixteen days of treatment with medicinal doses of iron and ammonium citrate.

The **therapeutic dosage** of iron in anemias should supply rather large quantities, so that the restoration may be accomplished promptly. The increase of hemoglobin should be no less than 1 per cent per day, if the original level was below 50 per cent. This amount of hemoglobin contains about 24 mg. of iron, and this quantity of iron suffices if it is administered parenterally (Heath, Strauss and Castle, 1932), *f. i.*, as iron and ammonium citrate; but since absorption is incomplete and varies for different individuals and different preparations, considerably larger quantities must be given by mouth, from 50 mg. to more than 1000 mg. of iron per day, usually about 200 mg. per day when administered as ferrous iron.

The *utilization of clinical iron medication*, with the modern full oral dosage, in hypochromatic anemias has been compared by Fullerton, 1934, on the basis that a rise of 1 per cent of the hemoglobin level contains about 24 mg. of iron. The results as shown in the table demonstrate that the four preparations studied gave practically the same improvement if effective doses were used. The difference of dosage corresponds to the difference in utilization, which was highest for the soluble ionized salts, less for the carbonate, and lowest for the citrate. On the basis of this table, the *effective daily dosage* (to utilize 30 mg. of iron) would be about 1500 mg. of reduced iron, assuming the absorption as 2.5 per cent. Tincture of ferric chloride, containing 4.5 per cent of iron, and assuming 20 per cent absorption, would require 3 cc. per day. The daily parenteral dose of the citrate, with 100 per cent utilization, would be 0.2 Gm.

Modern Dosage of Iron Compounds

Compound	Daily dose in Gm.	Fe content of daily dose in mg.	Utilization of daily Fe per cent	mg.
Iron and Ammonium Citrate	6.0	1215	2.5	30.4
Ferrous Sulfate, Exsiccated	0.6	180	15.7	27.2
Ferrous Carbonate Mass*	2.0 (U.S.P.) 3.0 (B.P.)	330	7.5	25.0
Ferrous Chloride, as pills	0.4	180	18.0	32.4

*Equivalent to ten Blaud's pills.

Until recent years, these preparations were generally used in an eighth to half of the above daily doses: six Blaud's pills; 2 cc. of tincture of ferric chloride; 0.2 Gm. of reduced iron; and 0.75 Gm. of the citrate by mouth, 0.1 Gm. hypodermically. This may account for the discredit into which iron therapy had fallen until it was reinstated in more effective form by better controlled observations.

In nutritional anemia of *infants*, 10 mg. of Fe per day suffices if administered as ferrous chloride, but 750 mg. are required as ferric ammonium citrate. Older children require 50 to 200 mg. as ferrous chloride (Lucas and Summerfeldt, 1939).

Choice of Iron Preparations; Administration.—The demonstration of the therapeutic effects of iron was first made with inorganic forms. Sydenham, 1661, in the treatment of chlorosis, used a wine of iron, but chiefly the chalybeate mineral waters, as "more congenial to nature"; Blaud in 1831 introduced his famed pills of ferrous carbonate; many other iron salts had demonstrated their clinical usefulness in the treatment of chlorosis before the "food-iron" theory came into vogue (about 1885). Notwithstanding the polemics of Bunge, clinical experience continued to confirm that the inorganic preparations are more effective than the organic. Even the insoluble carbonate (Blaud's pill) or reduced iron are readily dissolved by the gastric hydrochloric acid. The choice may therefore be determined chiefly by the differences in local action, by expense and by convenience. Solutions of ionized iron salts are astringent in the mouth, and attack and discolor the teeth, somewhat even when taken much diluted and through a glass tube. Their stains on silver spoons may be removed by ammonium hydroxide. The citrate in solution also blackens the teeth. These effects may be avoided by using the solid drugs in pills or capsules. They may also cause gastro-intestinal irritation, constipation and diarrhea, these being less with the citrate and least with the carbonate and reduced iron. The water-insoluble preparations require gastric acidity for their solution, and would therefore be less effective in hypochlorhydria. They should be taken just before meals, to secure maximal contact with the gastric acid, while the soluble iron salts are taken just after meals to minimize their local action. The citrate combines assured efficiency with a minimum of local action, but it is rather expensive. The ferrous sulfate and chloride are more economical, and can generally be taken as pills without serious inconvenience. They should be made into a mass with glucose, to protect them against oxidation, which renders them less effective (Reimann and Fritsch, 1930). A syrup of ferrous sulfate, containing 32 mg. of Fe per 4 cc., is described and recommended by Lucas and Summerfeldt, 1939.

There is no justification for using "organic" iron preparations. Hypodermic administration of iron and ammonium citrate (1 cc. of 10 per cent) should only be considered if oral administration is not feasible, for it is rather painful and sometimes produces severe local and systemic reaction, gastritis, and the like. These accidents have not been observed in animals even with much larger doses (L. W. Rowe, 1917).

IRON PREPARATIONS.—Only the most important preparations need be described. It may be remembered that ferric salts have a reddish, the ferrous a greenish, color. The most important *incompatibilities* are: alkalis, salicylates, phenol.

INSOLUBLE IRON PREPARATIONS.—***Reduced Iron,** U.S.P. (Ferrum Reductum), is iron reduced to the metallic state by the action of hydrogen upon ferric oxide. Very fine, grayish-black, lusterless powder, without odor or taste. Dose, 0.5 Gm., 8 grains, as powders or capsules. ***Ferrous Carbonate Pills,** U.S.P. (Blaud's, Chalybeate or Ferruginous Pills), contain 65 mg., 1 grain, of $FeCO_3$, made from ferrous sulfate and potassium carbonate. Contrary to the prevailing impression, the U.S.P. Blaud's pills are quite stable, and preferable to the proprietary substitutes (Warren, 1915). Dose, five pills. *Mass of Ferrous Carbonate,* U.S.P., *Vallet's Mass,* a pilular mass containing about 40 per cent of ferrous carbonate. Dose, 0.6 Gm. *Magma of Ferric Hydroxide,* U.S.P. (Arsenic Antidote; Ferric Hydrate with Magnesia); 40 cc. of Solution of Ferric Sulfate are diluted with 125 cc. of water. This is added, when needed, to 10 Gm. of Magnesium Oxide, or 300 cc. of Magma Magnesia diluted with water to about 750 cc. The dilute solution of ferric sulfate and magnesia mixture should be kept on hand in separate bottles, ready for immediate use, so that this antidote to arsenical poisoning may be quickly prepared. Dose, 120 cc., 4 ounces.

"SCALE SALTS" OF IRON.—***Ferric Ammonium Citrate,** U.S.P., a mixture of ferric citrate and ammonium citrate containing about 17.5 per cent Fe (20 per cent, B.P.), occurs as thin, transparent, garnet-red scales or granules without odor and having a saline, mildly ferruginous taste; deliquescent in moist air. Readily and completely sol. in water; reaction nearly neutral; insoluble in alcohol. Average dose, 1 Gm., 15 grains. *Ferric Ammonium Capsules,* U.S.P.; usual size, 0.5 Gm., 7½ grains. *Green Iron and Ammonium Citrates,* U.S.P. (Ferri et Ammonii Citrates Virides), 15 per cent Fe, occurs as green scales or granules having similar properties; very soluble in water, with acid reaction. Dose, by parenteral injection, 60 mg., 1 grain.

SOLUBLE FERROUS SALTS.—***Ferrous Sulfate,** U.S.P. (Green Vitriol); $FeSO_4 \cdot 7H_2O$, corresponding to about 56 per cent of anhydrous ferrous sulfate; large, pale green crystals; odorless, saline styptic taste; effloresces in dry air. Freely sol. in water (1:1.4) with acid reaction; practically insol. in alc. Dose, 0.3 Gm., 5 grains. The crude salt is employed as a deodorizer for fecal matter, but is not germicidal. *Exsiccated Ferrous Sulfate,* U.S.P., not less than 80 per cent of the anhydrous salt. *Dose,* 0.2 Gm., 3 grains. *Ferrous Sulfate Tablets,* U.S.P.; usual size, 0.3 Gm., 5 grains. *Ferrous Iodide Syrup,* U.S.P., 5 per cent of ferrous iodide, FeI_2, is a pale green acid liquid of strong iron taste. Very susceptible to oxidation, turning brownish. It combines the therapeutic properties of iron and iodides, and is often prescribed in goiter (2 drops, twice daily, gradually increased to 15 drops three times daily; Marine and Lenhart, 1911) and as a general tonic in "scrofulous" conditions. Average dose, 1 cc., 15 minims, contains about 52 mg., 0.85 grain, of iodine.

SOLUBLE FERRIC SALTS.—**Ferric Chloride Tincture,** N.F., about 13 per cent of $FeCl_3$ or 4.5 per cent of Fe, is prepared by mixing the liquor (solution) with alcohol. The U.S.P. IX directed it to stand three months before using, to permit the formation of esters. A bright, amber, acid liquid of slightly ethereal odor and astringent taste. Miscible with water or alcohol. Dose, 0.6 cc., 10 minims, diluted. Often used as local astringent in tonsillitis (equal parts of the tincture, glycerin and water). *Ferric Chloride Solution,* N.F., contains 30 per cent of the $FeCl_3$, or 10 per cent of Fe. Dose, 0.1 cc., 1½ minims. *Iron Subsulfate Solution* (Monsel's Solution, Sol. of Basic Ferric Sulfate) contains 21 per cent of Fe. Dose, 0.2 cc., 3 minims. Used mainly locally, as styptic. *Iron Tersulfate Solution,* N.F., contains 10 per cent of Fe as ferric sulfate. *Iron (Chalybeate) Mineral Waters* contain the iron most often as ferric bicarbonate; sometimes as sulfate, oxide and rarely as chloride.

ANTIANEMIC LIVER AND STOMACH PREPARATIONS

Liver contains a substance or complex necessary for the formation of blood in the bone marrow. The agent is formed in the stomach by the digestion of certain proteins, the "extrinsic factor," by some ferment, the "intrinsic factor." The product is absorbed and stored in the liver as the "active substance" of the liver. Its deficiency is "idiopathic," pernicious ("primary") anemia and in sprue impedes the orderly maturation of the megalocytes into reticulocytes, with secondary increased destruction of erythrocytes and hyperchromic anemia. This in turn results in degenerative anatomical changes in the central nervous system, perhaps as a result of the anoxia. The deficiency can be relieved completely by the administration of raw liver, liver extract, dried stomach and in most cases by folic acid, except for the anatomical nervous changes which have already taken place. The administration has no effect on normal individuals, but in these anemias it causes prompt resumption of the progressive development of the megalocytes, increased output of reticulocytes and steady rise of the red cell count and hemoglobin to the normal level, which is maintained as long as the administration is continued, but relapses when it is discontinued; except that a limited amount may be stored if large doses have been given, especially by a parenteral injection, when it may last some weeks. Oral administration is quite effective, but there are limits to the absorption, so that considerably larger doses are necessary. Interference of diarrhea with absorption may be a factor in the causation of sprue, while the hypochlorhydria of pernicious anemia may be a factor in diminishing the formation of the active complex. These antianemic preparations are also useful in some obscure anemias. In secondary anemias generally they have no effect unless iron is administered, when they hasten its transformation into hemoglobin and thereby increase its absorption. They are generally superfluous, but are valuable adjuncts when iron alone does not prove sufficiently effective. The active principle has not been definitely isolated. The potency of the preparations must be ascertained by actual trial on anemia patients by a standardized technic, established, reviewed and supervised by a special Advisory Board of the U.S.P.

Historical.—The treatment of pernicious anemia was unsuccessful and the course invariably fatal as the name implies, until the discovery of the specific antianemic action of liver. This started with the demonstration of Whipple and Robscheit-Robbins, 1920 and 1925, that dogs subjected to severe anemia by repeated hemorrhage assimilated iron more efficiently and recovered more rapidly on diets rich in liver, heart or skeletal muscle, or some other foods. The effect of liver was especially striking, and this came to be commonly added to the diet of patients suffering from various anemias, including the pernicious. The results were rather doubtful, until much larger quantities of liver were taken by a pernicious anemia patient under the care of G. R. Minot. Minot and Murphy, 1926, 1927, reported a considerable series of patients with this disease, in whom striking, prompt and lasting improvement resulted from diets including daily 250 to 500 Gm. of mammalian liver. Cooked liver is quite effective, although raw liver pulp may be more active. Kidney is also potent. An aqueous deproteinated extract ("*No. 343*") was found to be fully effective and suitable for clinical use (E. J. Cohn, Minot and Murphy *et al.*, 1927), even for intravenous injection. The common occurrence of gastric achylia in pernicious anemia suggests the possibility of a causal relationship. Castle, 1929, found that the feeding of beefsteak, which had been digested with normal human gastric juice, produced the same response as the liver preparations; predigestion by the ordinary commercial pepsins was ineffective. C. S. Sturgis and Isaacs, 1929, 1930, showed that the desiccated stomach of the hog is highly potent (about equivalent to an equal weight of the Concentrated Liver Extract 343). It acts even without added meat (Kandel, 1931).

Special Characteristics of Pernicious Anemia.—Pernicious or primary anemia, first described in 1849 by Addison as "idiopathic anemia," differs from other so-called "secondary" anemias not only in the absence of recognized cause, but in the failure to respond to the forms of treatment to which these are amenable. Iron therapy is totally ineffective in pernicious anemia; indeed, it appears that the untreated patients have more iron available than can be used in the diminished manufacture of red blood corpuscles, for the color index is high and the granular *reserve iron* of the liver and spleen is considerably increased (Rumpf, 1901), as is also the dissolved iron of the spleen (Erben, 1900). The *iron of the serum*, which is normally between 1 and 1.4 mg., median 1 mg., per 100 cc., rises to 1.5 mg. in the attacks of pernicious anemia, returning to about 1.1 mg. during recovery. The excretion of iron is increased, even for eleven weeks after remission (H. H. Ricker and Winters, 1930). The urinary excretion was said to remain normal (Queckenstedt, 1913). It is evident, therefore, that the disease does not depend upon deficiency of iron, but on an anomaly in the blood-corpuscle regulation. There is direct evidence for defective blood formation in an actual paucity of blood-regenerating cells of the hematopoietic system, and in megaloblastic hyperplasia of the bone marrow (F. W. Peabody, 1927; F. Koller, 1939); the increase of urobilinogen indicates that blood destruction is also increased. The disease is subject to spontaneous remissions. It is associated with characteristic digestive disturbance, especially gastric achylia, anorexia, and glossitis; and eventually with anatomic degeneration of the central nervous system, especially the sensory spinal tracts, leading to paresthesias. These nerve changes may perhaps be the result of deficient oxygen supply. The gastric disturbance may be concerned directly in the causation of the disease (Johansen, 1929).

The **therapeutic response** to effective liver or stomach administration in pernicious anemia starts with prompt and extensive, but temporary, increase of immature blood cells, the reticulocytes, in the peripheral blood; this is accompanied by a slower increase of mature red cells and of hemoglobin, which progress to the normal level. The megaloblastic hypertrophy of the bone marrow recedes to normal as the blood picture improves. The reticulocytes rise from the normal of 1 per cent or less, to 15 per cent or more, within five to ten days (Porter and Irving, 1929), then decline to the original level in about sixteen days when the restoration of the mature red cells is only half completed. This is distinctly improved within ten days, and attains to nearly normal generally within three weeks. With adequate and continuous dosage the improvement is certain. The response may be checked by complications, such as infections, but failure to respond within four weeks throws doubt on the diagnosis. Relapse occurs only if the administration is intermitted.

The *stimulation of the bone marrow to maturation of th megaloblasts* is confirmed by the response of healthy grain-fed *pigeons*, which normally have a megaloblastic condition of the bone marrow and a 10 per cent reticulocyte count. In these, the liver preparations, and their analogues, by mouth or vein, produce an increase of reticulocytes and diminution of the megaloblastic tissue. In contrast to pernicious anemia, the increase of reticulocytes is maintained, and there is no increase of erythrocytes. The difference may be attributed to the fact that the megaloblastic condition is normal for pigeons, and is, therefore, not abolished, but merely modified by treatment. The effect is specific for active preparations (including beefsteak); it is not produced by iron or histamine, or by inactive extracts (J. F. Vaughan, Muller and Zetzel, 1930). The excretion of *endogenous uric acid* is increased during the liver treatment in pernicious anemia (not in normal individuals), presumably by destruction of the red cell nuclei (M. C. Riddle and Sturgis, 1929).

Infections interfere with the response to liver therapy. This holds also for *pigeons:* infection with virulent Staphylococcus aureus decreases the normal reticulocyte count to half or lower, and prevents a good reticulocyte response to the injection of liver extract (G. L. Muller).

Responses of Other Anemias.—Liver or stomach therapy is as effective in *sprue* as in idiopathic anemia. It is also effective in *pellagra,* in conjunction with vitamin therapy (T. D. Spies, 1934), and in *tapeworm* anemia as adjuvant to iron (Birkeland, 1932). Clinical *secondary anemia* improves most rapidly if the iron therapy is supported by liberal diet and liver therapy, preferably by weekly parenteral injection of liver extract (Powers and Murphy, 1931; Murphy, 1933; review, West, 1935).

Liver has generally proved ineffective in the anemia of rice diet and fasting in pigeons (G. L. Muller, 1927, 1929; Barlow, 1930); in the bartonella anemia of rats (Neumann, 1930); and in entameba anemia of dogs (Kagy and Faust, 1930). With phenylhydrazine anemia in rabbits, no response was obtained by Adlersberg and Goldsegen, 1920, but Wright and Arthur, 1930, reported benefit. Paschkis and Taylor, 1934, reported it ineffective against phenylhydrazine, but effective against saponin anemia in rabbits.

The gastric factors furnish the starting point of the hematopoietic substance. This is formed by the digestion of meat and certain other protein foods with an unidentified enzyme present in the *intrinsic factor* of normal gastric juice of man and other mammals, but not in the gastric juice of pernicious anemia patients or in acidified solutions of pepsin (Castle, 1929). Idiopathic anemia is caused by partial or complete lack of this intrinsic factor in the gastric juice. It may be exaggerated by inadequate supply of *extrinsic factor* in the diet; and by failure to absorb the active substance from the digestive tract, or by its destruction there, so that oral administration of stomach or liver preparations may be ineffective, while parenteral injection of liver extract is effective; which is not uncommon in advanced cases (review, Castle, 1935).

Gastric juice does not contain the active principle, unless it has been in contact with extrinsic factor (Castle and Ham, 1936). *Extracts of the gastric mucosa* are also ineffective (Henning and Stieger, 1930), but become effective by incubation with extrinsic factor (Conner, 1931). Acidulated extracts of all regions of the stomach contain active substance if they include the muscular coat, which furnishes the extrinsic factor. It is abundant in dried *excised stomach,* if desiccated below 70° C. (Sturgis and Isaacs, 1929), being doubtless formed by self-digestion, the gastric muscle serving as extrinsic factor. Pylorus preparations are highly active, the fundus inert, the reverse of their content of pepsin and rennin (Meulengracht, 1935); but excision of the entire gastroduodenal portion of the stomach (Bachrach and Fogelson, 1937), or indeed of the entire stomach from dogs, does not lead to pernicious anemia, even after six years.

The *intrinsic gastric factor* is inactivated at 70° C., in solution and is presumably an enzyme (Strauss and Castle, 1932), but it has not been identified with any known constituent of gastric juice. It is not pepsin, rennin, lipase or hydrochloric acid. It is absent from normal saliva and duodenal juice and from the gastric juice in pernicious anemia, even when this contains normal amounts of acid and pepsin; it is present in the gastric juice of achlorhydria, if this is not caused by pernicious anemia (review, Castle, 1935). Exposure of normal human gastric juice to *p*H 10 for thirty minutes destroys its peptic activity without markedly affecting the intrinsic factor (Flood and West, 1936). The *extrinsic or food factor* resists autoclaving and is soluble in 80 per cent alcohol. It may be furnished by muscle, eggs, autolyzed yeast, rice polishings, wheat germ, spleen pulp, liver (fraction G); not by casein, wheat gluten or nucleic acid (Castle, 1935). *Digestion of liver extract* or its "G" fraction with stomach or gastric juice increases the activity three to seven times, permitting smaller dosage (Walden and Clowes, 1932). Autolysis of liver was reported to increase its activity (Herron and McElroy, 1933), implying that it may furnish the intrinsic as well as extrinsic factor. It has therefore given rise to some controversy (1937).

Liver Extract and Active Substance.—The continuous consumption of large quantities of liver is inconvenient and generally distasteful. E. J. Cohn, Minot and Murphy, and their associates, 1927, found that the activity is retained by deproteinated aqueous extracts, which may be greatly concentrated and are not disagreeable to take. "*Liver Extract No. 343*" is a powdered concentrate of this sort; several other liquid extracts for oral and for parenteral administration are on the market.

The *active substance* is soluble in water and dialyzable, insoluble in absolute alcohol, somewhat soluble in acidified alcohol, and in fat solvents. It is destroyed by strong alkalis and acids, not by boiling. It is free from protein, iron, carbohydrates and lipoids. Its nature has not been identified, but the properties point to polypeptide structure (Dakin and West, 1935; reviews, West, 1935; Y. Subbarow, Hastings and Elkin, 1945). It contains 10.6 per cent of nitrogen, but does not give the biuret reaction. Its hydrolysis yields beta hydroxyglutamic acid and l-gamma hydroxypyroline. Later evidence (B. M. Jacobson and Subbarow, 1937, 1941) indicates that the activity is not due to a single substance, but to a complex of at least four chemical entities. The primary factor, not chemically identified, produces submaximal reticulocyte response, but does not increase the erythrocytes when administered alone. The full response requires three accessory substances which are inert when given without the first substance. They have been identified as derivatives of tyrosine, purine and peptide, respectively.

Other Liver Extracts.—Several other kinds of active extracts are prepared from liver: for instance, Heparin, which prevents the coagulation of blood; another extract, which lowers the blood pressure on intravenous injection by a shock reaction, has been suggested against hypertension and eclampsia; it would appear a dangerous agent.

Standardization and Dosage.—The activity of liver extracts and also of stomach preparations varies widely, even if prepared by the same method, so that they must be standardized. This is done clinically on patients with pernicious anemia, by the reticulocyte response and by the rise of hemoglobin, as no other reliable method is available. The U.S.P. Anti-Anemia Preparations Advisory Board "*unit*" is the smallest amount which, given daily to patients with pernicious anemia, produces a satisfactory hematopoietic response, according to the criteria prescribed by the Board. The strength of the preparation is shown by the amount which must be administered to produce this effect, which is then the minimal daily dose, whether given daily or in multiple amounts with longer intervals. Larger amounts are often administered. In general, the oral unit would be contained in 300 to 400 Gm. of fresh liver, 30 to 40 Gm. of desiccated stomach, 13 to 25 Gm. (3 to 6 level teaspoonfuls) of dry liver extract, and widely varying amounts (but not less than 1/15 cc.) of the solutions intended for parenteral injection. The latter are not interchangeable with the oral preparations, since the factor of absorption enters into the assay, for ordinarily about thirty and up to seventy times more is required by mouth than hypodermically. The unit therefore applies to the method of use. Even with oral use, the potency of the extracts does not necessarily correspond to the amount of liver from which they have been produced.

Standardization on animals would be desirable and has been attempted, especially on pigeons (Wakerlin *et al.*, 1936) and on guinea pigs (B. M. Jacobson, 1934, 1936), but the results are not sufficiently consistent. Isolated bone marrow was proposed by N. Pace *et al.*, 1942.

Administration.—*Dry liver extract* occurs as a yellow water-soluble powder of not unpleasant taste. It is administered orally in water, soup, orange juice or other vehicle. *Liquid liver extracts* for oral use are also marketed. *Desiccated stomach* (ventriculin) is administered similarly. The therapeutic response is identical with that to the liver extract, quite as uniform, and perhaps even somewhat prompter (Rosenow, 1930; Wilkinson, 1930). *Parenteral administration of antianemic liver extract* is more effective than oral (Strauss, Taylor and Castle, 1931; W. P. Murphy, 1932) and is preferred in patients who are critically ill, especially to arrest spinal degeneration; where oral administration is not sufficiently effective; or when distaste is invincible. The smaller dosage renders it more economical. The solutions especially prepared for this purpose may be injected intramuscularly or intravenously, but the latter sometimes causes serious shock reactions, especially if the extracts are not sufficiently pure (Castle and Taylor, 1931). *Intramuscular injection* can be used without hospitalization and with relatively little discomfort. There may be pain, extending along the leg; sometimes fever of 99° to 102° F.; but no allergic reactions or erythema (Murphy, 1932). (Intradermal injection may produce severe reactions; J. G. McSorley and Davidson, 1944.) The parenteral injections are usually given in sufficient amount so that they need be repeated at intervals of one to three weeks, for maintenance. With massive doses, intramuscularly, the effect may last two to eight months (F. H. Miller, 1937), so that there is evidently effective storage. The substance passes across the placenta, for it is plentiful in fetal calves' liver (Wigodsky *et al.*, 1938).

PREPARATIONS.—***Liver Extract,** U.S.P. (Extractum Hepatis; Dry Liver Extract); "contains that soluble thermostabile fraction of mammalian livers which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia." The average dose, corresponding to one U.S.P. unit, is to be stated upon the label of the container. *Liver Solution,* U.S.P., contains 12 to 25 per cent alc.; not more than 40 per cent of glycerin. Conforms to the U.S.P. specifications. Dose, to be stated upon the label of the container. ***Liver Injection,** U.S.P., **Purified Liver Solution,** is a sterile watery solution prepared for parenteral use. Conforms to the U.S.P. specifications. May contain not in excess of 0.5 per cent of cresol or of phenol; ampuls of 2, 5, 10 and 15 units in one cubic centimeter. *Liver with Stomach,* U.S.P., a dry mixture of liver extract and minced hog stomach. Its potency is higher than that of its separate components; the average dose, however, corresponds to one U.S.P. unit. ***Powdered Stomach,** U.S.P. (Stomachus; Ventriculin), is the dried and powdered defatted wall of the stomach of the hog. It contains that antianemic factor which causes an increase in the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. Conforms to specifications as outlined by the U.S.P. The activity is readily destroyed when the preparation is suspended in hot liquids.

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FOLIC ACID (PTEROYL-GLUTAMIC ACID)

Folic acid, M vitamin, Lactobacillus casei factor (also named $B_{10, 11}$, c and factors U, R and S), is a constituent of the B vitamin complex, which has been crystallized and synthesized (R. B. Angier *et al.*, 1945; R. B. Angier, Boothe *et al.*, 1946; J. H. Mowat, 1946). The therapeutically active form of synthetic pteroyl-glutamic acid is pteridyl-p-aminobenzoyl glutamic acid, abbreviated as *pteroylglutamic* acid. This is the form marketed as *synthetic folic acid.* Several clinically inactive modifications contain additional molecules of glutamic acid.

Folic acid has antianemic actions closely resembling those of liver, but not quite identical. Striking clinical effects against macrocytic anemia, pernicious anemia and sprue have been reported by T. D. Spies, 1946; C. V. Moore *et al.*, 1946; R. W. Heinle and Welch, 1947; G. A. Goldsmith, 1947; and others. It is not effective in any condition in which liver is ineffective; the restoration of the blood picture is often not complete. In some patients it does not prevent neurologic relapse even when the blood picture is restored; indeed, it appears as if the folic acid actually precipitated the neurologic manifestations in some cases. It should therefore be used only as adjuvant to liver therapy in pernicious anemia. It is employed especially in sprue. Oral administration is equally effective as parenteral, or more so. Folic acid appears essential to all types of bone marrow cells. It stimulates hematopoiesis and growth in rats, chicks and guinea pigs.

Historical.—P. L. Day *et al.*, 1935, observed that Rhesus monkeys on restricted diet developed a deficiency disease which was cured by some special factor in yeast and liver extract which they called *M vitamin.* P. L. Day *et al.*, 1945, also found this essential for the growth of *Lactobacillus casei*, and necessary for normal growth and hemoglobin formation in chicks.

Occurrence.—The name folic acid was derived from spinach leaves, one of the earlier sources. It occurs in liver, but highly purified potent liver extracts contain only ineffective traces. Folic acid is also present in many other foods, chiefly in the conjugated forms, which appear inactive in anemia, although they seem to suffice for normal protection (A. D. Welch, Heinle *et al.*, 1946).

Toxicology.—Folic acid is almost devoid of side actions even when doses far above the clinical equivalent are continued for long periods. It is not irritant hypodermically, has no effect on the blood sugar level, and has a feeble action on isolated intestines. The acutely lethal dose exceeds 200 mg. per Kg. (Harned *et al.*, 1946).

Deficiency Phenomena.—Folic acid has been shown to be a dietary essential for chickens and turkeys, rats, mice, guinea pigs, dogs, monkeys and man. Its deficiency produces stunted growth, anemia, leukopenia, granulocytopenia, digestive disturbances, spastic cervical paralysis, dermatoses, achromotrichia, perosis. The defect probably enters into some phase of nitrogen metabolism, perhaps in the synthesis of thymine (review, F. S. Daft, 1946). T. D. Spies, Vilter *et al.*, 1946, report that *thymine* appears as successful as folic acid in pernicious anemia.

Deficiency of folic acid can be induced in rats by adding 1 per cent of succinyl sulfathiazole to the food, presumably inhibiting the normal synthesis of folic acid by intestinal bacteria. The effects can be prevented or corrected by adding folic acid to the diet (K. M. Endicott and Ott, 1945). Deficiency in monkeys produces the effects of deficiency of the antianemic liver factor (J. M. Cooperman, Elvehjem *et al.*, 1946). Acetylcholine hyperchromic anemia in dogs is cured by folic acid, as by liver extract. Both increase the cholinesterase activity of the blood (J. E. Davis, 1946).

Clinical Results.—T. D. Spies, 1946, reports prompt hematopoietic response, increase of reticulocytes, erythrocytes, and decrease of the megaloblasts of the bone marrow, on parenteral or oral administration of synthetic folic acid in the macrocytic anemias of pellagra, pernicious anemia, sprue and pregnancy. It is ineffective against aplastic anemia, leukemic anemia, and iron deficiency anemia. It improves nutritional neutropenia, but not that of infectious diseases or idiopathic conditions. It is supposed to accelerate the development of immature erythrocytes in the bone marrow (C. C. Sturgis, 1946); but it does not mature the primitive red cells *in vitro*, as does antianemic liver extract (E. E. Hays, 1946). Folic acid would be especially useful for patients who do not tolerate liver. The maximal response may often be procured by 10 or 20 mg. daily by mouth, and can generally be maintained with 2.5 to 10 mg. daily. No untoward symptoms were produced by 400 mg. daily. W. J. Darby and Jones, 1946, obtained complete hematologic response in nontropic sprue from daily intramuscular injections of 15 mg. C. V. Moore *et al.*, 1946, find that the potency is quantitatively less than some of the liver extract fractions. At least 5 mg. parenterally are required for maximal response, sometimes 100 mg. The potency is not increased by incubation with gastric juice.

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GERMANIUM

The injection into rabbits of the dioxide of this rare element causes some increase of the blood cells, attributed to stimulation of the bone marrow (Hammett *et al.*, 1922; J. H. Muller and Izsard, 1922; Beard, Myers *et al.*, 1931). This does not occur in rabbits (Minot and Sampson, 1922), and no significant effects have been observed in any type of clinical anemia (Garvin, 1922; Alexander, 1923).

Plants absorb germanium if it is added to the soil. Small amounts stimulate their growth, large amounts are toxic. The mould Aspergillus niger can take up and store large quantities without being poisoned (Geilmann and Brünger, 1935).

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MANGANESE

This metal resembles iron chemically and occurs widely distributed in nature. Small amounts are present in all animal and plant tissues, and appear essential for growth and reproduction, probably as oxidative catalyst. The absorption is limited, so that it does not produce acute effects other than local, the latter especially as the oxidative, antiseptic and astringent effects of potassium permanganate, the form in which it is principally employed in medicine. Continued administration of manganese assists in the assimilation of iron into hemoglobin. Prolonged exposure to excessive quantities of manganese, especially in the form of dust, leads to an industrial manganese toxicosis, with prominent cerebral symptoms, mental and ataxic (review, Fairhall and Neal, 1943).

Potassium permanganate, $KMnO_4$, in the presence of organic matter splits readily into MnO_2 (forming a brown precipitate) and active oxygen. It is therefore an effective oxidizing agent and disinfectant, but its efficiency is limited by any excess of organic matter. Its action is only superficial, and it is markedly irritant. It is used as an antiseptic for *mucous membranes and the skin*, in dilutions of 1:10,000 to 1:100; especially in the urethra (1:4000 to 1:1000). Hot irrigation with this solution is followed by catarrhal secretion which is supposed to clear the gonococci. A 1:5000 solution is said to be a satisfactory anesthetic for introducing urethral sounds (Barton, 1913). Beck, 1913, recommended it against *burns* (1:4000 to 1:3000 on gauze and as lotion). As a *mouth wash*, one or two crystals may be added to a tumbler of water, enough to give a rose or claret color. *Tablets* of 0.03 Gm. are convenient for these uses. *Ringworm and bromidrosis of the foot may be treated by soaking* half an hour daily in a basin of hot water with permanganate, a tablet per pint. The *brown discoloration* of the skin, due to reduction products, may be removed by vinegar or lemon juice. A saturated solution may be employed for disinfecting the hands, followed by 1 per cent oxalic acid solution to remove the stain. It is effective against *snake bite*, but only if used within five minutes (1 per cent, applied to free incisions after double ligature, if possible; Weidenmann, 1915; A. M. Reese, 1934). Permanganate has been widely used as a general *antidote to organic poisons* before they leave the stomach, but its usefulness is limited by the presence of food in the stomach and by its own toxicity. Concentrated solutions are caustic, and even fairly dilute solutions are quite irritant. Large doses may produce fatal gastro-enteritis. The concentration should not exceed 1:2000 if a tumblerful is administered; 1:10,000 may be used for lavage; none should be left in the stomach. It should not be relied upon to destroy all the poison, but the stomach should be evacuated. It may be quite *effective* against a number of alkaloids, including aconitine, morphine and strychnine; also against picrotoxin, amidopyrine and antipyrine. It is useless against atropine, cocaine, phosphorus, and most hypnotics and of little use against cyanides. Phenol would require larger doses than can be used (Hatcher, 1935).

Intravenous injection of permanganate causes immediate intense hemolysis and capillary injury. It is reduced, first to colloidal manganous oxide, MnO, and finally to the dioxide, MnO_2 (Sabbatani, 1928).

Smooth muscle is stimulated by direct contact with permanganate, 0.02 to 1 per cent; perfused blood vessels of guinea pigs are constricted as with epinephrine; excised *intestine* of rats and rabbits responds with increased tonus, which may be inhibited by atropine. Excised *uterus* of guinea pigs also gives prolonged increase of tonus, which is relaxed by epinephrine, but not by atropine (de Jongh, 1933). Oral administration to rabbits, 1 to 2 cc. of 1 per cent, also increased uterine activity; daily administration caused death of the embryos in pregnant guinea pigs, and abortion in pregnant mice (de Jongh, 1933), presumably secondary to gastroenteritis.

Intravenous injections of manganese chloride, $MnCl_2$, were introduced in schizophrenia (1 to 8 cc. of 1:400 solution, twice weekly for ten weeks). They cause some flocculation reaction, which probably accounts for whatever therapeutic effects may have resulted. English, 1929, claimed marked improvement in the mental and physical condition of over half of the patients, but later observers do not seem to have obtained these favorable results. Oral administration and intramuscular injection of colloidal manganese are ineffective (R. G. Hoskins, 1934). Bargero, 1906, found manganese toxic by vein, and observed fatty degeneration of the liver. A variety of *skin diseases*, especially acne, furunculosis and sycosis, have been reported benefited by injection of manganese preparations (E. L. Oliver and Crawford, 1936), but further trials proved quite unsatisfactory (M. Sullivan, 1940).

Occurrence of Manganese.—Traces occur naturally in all organs, in man and various animals, and much more in plants, its presence being fairly constant in the same species (Bertrand and Medigreceanu, 1912). The daily income for man is about 10 mg. The amount in *wheat* is about equal to the iron (Headdon, 1915). Dried wheat grain contains 2.7 to 4.7 mg. per 100 Gm., depending on the soil; the greater part is in the bran (Javilliers and Imas, 1927). Whole wheat flour averages 3.5 to 4 mg. per 100 Gm.; patent flour, only 0.4 mg.; white bread, 1.1 mg. per pound; whole white bread, 11 mg. (C. Hoffman *et al.*, 1943). The *manganese of animals* is derived partly from vegetable, but mainly from animal, food; it does not disappear from the body even on manganese-free food. Mammals contain only one-tenth to one-fifth as much as other classes of animals. The content of the human liver and kidneys is practically constant throughout life (Brückmann and Zondek, 1939).

The manganese content of normal human blood averages 0.014 mg. per cent; of urine, 0.01 mg. per liter (W. C. Dreesen and Sievers, 1946).

Fate.—Manganese is *absorbed* to a slight degree from the alimentary canal, being *deposited mainly* in the liver and kidneys, and passing also to the fetus *in utero*. Its *retention* in preschool children is proportional to the amount ingested (Everson and Daniels, 1934). After intravenous injection of radioactive manganese the highest concentration by far is in the liver and kidneys; that in the brain is only a seventieth of the liver (H. J. Born *et al.*, 1943). Bone retains very little (M. S. Mohamed and Greenberg, 1943). Its *excretion* appears to take about the same course as iron (Harnak and Schreiber, 1901). After oral ingestion it appears as black sulfide in the feces. The absorption is slight (Bargero, 1906). Benedetti, 1906, and Piccinini, 1910, 1912, claimed that it increases the reserve iron. Benedetti also investigated the fate after subcutaneous injection of the citrate. *The excretion after intravenous or peritoneal injection* of radioactive manganese is almost entirely fecal; almost half of this is through the bile (D. M. Greenberg *et al.*, 1943). The excretion of bile is diminished by blocking the reticulo-endothelial cells with India ink, as is also the case with Fe, Ni and Co (Iwai, 1930).

Manganese deficiency phenomena in mammals consist in interference with growth and reproduction. They have been studied especially on *rats*, with synthetic diets practically freed from Mn. Impaired growth and slight progressive anemia develop when the daily income is reduced to 0.005 mg. (L. W. Wachtel *et al.*, 1943). The addition of 0.03 mg. of MnO_2 daily increased growth by a third over the controls; 0.9 mg. gave less growth than the controls, although the animals ate as much (McCarrison, 1927). Manganese deficiency diminishes the arginase concentration of the liver. The estrous cycle may be irregular or suppressed. Testicular degeneration and lack of spermatozoa production result in sterility. No histologic abnormalities are observable in the adrenals, kidneys, pituitary or thyroid; the ascorbic acid content of the tissues is normal (P. D. Boyer, Shaw and Phillips, 1942). *Mice* show little effect on growth, but the males become sterile, the young nonviable. All the changes in rats and mice can be reversed by administering manganese (M. E. Shils and McCollum, 1943). *Mn deficiency phenomena in chicks* are much more marked, resulting in "perosis" or "slipped tendons," shortness of legs, wings, spinal column and beak. This is said to occur also in chicks hatched from the eggs laid by Mn-deficient hens (C. D. Caskey *et al.*, 1944). It is not due to general growth retardation, nor to rachitis. The ash content of the bone is significantly lower than normal. It is remedied by adding Mn to the food, more effectively if the Ca and P income is relatively high. Hypodermic injection is more completely effective, with smaller doses (Schaible *et al.*, 1938; Insko *et al.*, 1938; Caskey *et al.*, 1939). If the diet remains deficient in Mn, the addition of Ca and P increases the perosis, probably by making the Mn less soluble (Wilgus and Patton, 1939). Sunlight decreases the deficiency phenomena (Christiansen *et al.*, 1939). When radioactive manganese is administered to deficient chicks it is excreted as in the controls (M. S. Mohamed and Greenberg, 1943). Small amounts of manganese and other elements, especially zinc and boron, increase materially the *growth of plants*. This is easily measured on cultures of the mould Aspergillus niger. It has been suggested that they act by killing competing or infective bacteria, but they appear to act directly (Bertrand, 1912).

Enzymes.—Manganous chloride accelerates autolysis when added to excised liver (Bradley and Morse, 1915). Manganese is essential for the oxidase concerned in plant color changes. It has been suggested that it is necessary for the utilization of thiamine.

Manganese Toxicosis.—Chronic poisoning results from exposure to the dust or fumes of any of its compounds in the industries, in zinc mines, grinding, and so forth (review, L. T. Fairhall and Neal, 1943). R. Kawamura *et al.*, 1940, reported a group intoxication from water of a well near which a large number of dry cells had been buried. The susceptibility varies considerably. The phenomena are due to severe atrophic changes in the basal ganglia, with symptoms closely resembling those of Parkinson's disease. They generally start insidiously in one to three years, sometimes three months after the beginning of the exposure, with languor, sleepiness, weakness of the legs; then fine tremors or gross rhythmical movements, marked emotional disturbances, uncontrollable laughter or crying, impulsive acts with a background of euphoria; then slowly progressive motor ataxia, usually without sensory disturbance; a peculiar stiffness of the muscles, with jerky walk; difficulty in speech, deglutition and facial expression, cramped handwriting; other muscle groups may become involved. The workers are reported to be more susceptible to pneumonia. Industrial workers exposed to inhalation of manganese oxides have a high incidence of respiratory inflammations, nasopharyngitis, bronchitis and pneumonia (T. A. L. Davis, 1946). Destruction of ganglion cells of the basal ganglia involving the thalamus and caudate and lenticular nucelus is responsible for most of the symptoms. The spinal cord and the peripheral nerves may also be affected (H. Voss, 1942). The prognosis is good as to life. Early cases recover spontaneously, more or less, when removed from exposure; the psychoses generally disappear slowly but completely; the neurologic symptoms persist in almost every case, and advanced symptoms cripple permanently, especially the legs. There is no effective treatment except prevention. The maximal permissible concentration in air has been tentatively placed at 6 mg. per cubic meter (review, L. T. Fairhall and Neal, 1943). The condition is not observed in the uses of manganese that do not involve dust; nor is it produced in animals by oral administration (von Oettingen and Sollmann, 1926), but this results in hepatic cirrhosis, preceded by excessive rise of blood sugar after administration of levulose or galactose. Manganese administration to rats decreases the time required by p-*dimethylaminoazobenzene* to produce liver tumor. This effect is not produced by Cu, Zn, Co or iodine (G. R. Sharpless, 1945). *Permanganate poisoning* may cause nephroses.

Preparations—*Potassium Permanganate, U.S.P.; $KMnO_4$; occurs as slender, dark purple prisms; odorless; astringent taste. Sol. in water (1:15); decomposed by alc. and all organic matter, and explosive. Dose, 0.06 Gm., 1 grain, U.S.P.; 0.06 to 0.2 Gm., 1 to 3 grains, B.P.; diluted.

Mangani Dioxidum Praecipitatum (Mangan. Diox. Praec.) consists chiefly of manganese dioxide (MnO_2). Prepared by precipitating manganese sulfate by ammonia in the presence of hydrogen dioxide. Heavy, fine, black powder, without taste or odor; insol. in water or alc. Dose, 0.25 Gm., 4 grains.

RHENIUM

Physiological effects have been studied by P. P. Cohen, 1940.

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CHROMIUM

Uses.—Chromium trioxide (chromic acid), CrO_3, is used externally as caustic. It and the chromates have some toxicologic importance, the *dichromate*, $K_2Cr_2O_7$, being used in dyeing and in "battery fluids." They produce a characteristic *nephritis* and glycosuria.

Chromic acid ulcers are an important industrial hazard in chromium plating.

The hydrogen evolved in the chromic acid bath carries up a fine spray of the liquid. This causes rhinitis, terminating in perforating ulcers of the nasal septum. Continued daily exposure to 1:10,000 of air suffices for this. The skin of the exposed hands and forearms may also be involved, with diffuse dermatitis, progressing to simple or multiple ulceration ("chrome holes"), but generally only if there has been previous abrasion. The ulcers develop slowly, but are deep and painful, with sloughing of the entire thickness of the skin and slow separation of the slough, with scarring. If they are not treated, they last indefinitely and may spread; but when the base is cleared, healing is fairly rapid and complete. *Prophylaxis* consists in transverse artificial ventilation to carry the spray away from the operator; rubber gloves and care as to any fissures and abrasions; protection of the inside of the nostrils and exposed skin by an ointment applied several times daily (petrolatum, preferably with 25 per cent of hydrous wool fat); washing with 5 per cent sodium thiosulfate ("hypo") (L. Schwartz, 1939).

Zinc chromate used as primer for paint, often produces gradual sensitization, persisting or increasing with continued exposure. A. F. Hall, 1944, reports that it was responsible for two-thirds of the dermatites among aircraft workers. The average time of exposure was seven months.

Acute peroral chromate poisoning exhibits corrosive effect and nephritis, with death in one to forty-eight hours. The symptoms begin with sore throat, vomiting, diarrhea, albuminuria and hematuria. Nervous symptoms develop. The blood pressure is low. Hemorrhages occur into the gastro-intestinal or respiratory tract. Less than 0.5 Gm. of potassium dichromate may cause serious poisoning, and the fatal dose is below 8 Gm.; of chromic acid, 6 Gm. The *treatment* is by evacuation and demulcents (review and bibliography, Rabbeno, 1933).

Fate.—When bichromates are given by mouth, they are reduced to chromous oxide and partly deposited as such in the organs, the rest being excreted by the urine (Kappeler, 1896). Bichromate transforms *hemoglobin* into methemoglobin *in vitro* (Mattucci, 1933).

Chromate nephritis is produced experimentally by hypodermic injection of the chromates. It is mainly tubular, but the glomeruli are involved first. All the phenomena are similar to those of uranium (including retention, glycosuria, chronic nephritis, and so forth), except that edema is not common (Gergens, 1876; Hellin and Spiro, 1897; Schlayer and Hedinger, 1907; Ophüls, 1908; Austin and Eisenbrey, 1911; R. M. Smith, 1911; Folin, Karsner and Denis, 1912; MacNider, 1912; Eisenbrey, 1913; E. Franck, 1913; glycosuria, Mosenthal and Schlayer, 1913; diuretics, and so on).

Internal Therapy.—Kolipinski, 1902 and 1908, reported favorable results from chromium sulfate (8 grains, three to four times daily) in neurasthenia, tabes and other nervous conditions. They have not been adequately confirmed.

PREPARATIONS.—*Chromium Trioxide*, U.S.P. (Chromic Acid; Chromic Anhydride); CrO_3; occurs as dark red, needle-shaped crystals, deliquescent and very sol. in water (1:0.6). *Explosive* with all organic matters. Used as a caustic, solid or in solution (1:1; as astringent (2 to 3 per cent); for urethral injections (1:2000 to 4000); and against sweating feet (5 per cent).

ALUMINUM

The soluble salts are strongly precipitant to proteins, and therefore astringent, styptic and antiseptic, but not corrosive to intact skin or mucosae. They are used externally and sometimes against diarrhea, the hydroxide also as antacid and protective in gastric ulcer. Very little is absorbed from the alimentary canal. Even large doses cause only vomiting and diarrhea, or local exudative inflammation and no direct systemic effects. The quantities which may be dissolved from aluminum cooking vessels, even by dilute acids, are too small to be of any importance. Alum baking powders also appear to be harmless.

Precipitant and Astringent Action.—A 1 per cent solution of alum precipitates proteins, and most colloidal suspensions. This is employed for clarifying turbid water. The protein precipitation is also used in the purification of toxins and antitoxins. The protein precipitates tend to redissolve in excess of protein. The precipitation or gelation of serum proteins is maximal with 8 per cent of aluminum acetate; this also produces maximal contraction of excised rat tendon (W. Straub, 1926). The astringent action was studied by Barinetti, 1914.

Local Use on Skin.—Solution of Aluminum Acetate, N.F. (Burow's Solution), containing about 5 per cent of neutral aluminum acetate, $Al(C_2H_3O_2)_3$, and the somewhat less astringent and less irritant *Solution of Aluminum Subacetate,* N.F., containing nearly 8 per cent of basic aluminum acetate, $Al(C_2H_3O_2)_2OH$, are used in dermatitis and burns. Both require dilution with 5 to 10 parts of water. A 1 per cent dilution of the acetate solution was reported to be antiseptic, and 5 per cent germicidal (Kuehl, 1913). *Alum* (potassium or ammonium and aluminum sulfate), as 1 per cent solution, is somewhat more irritant. A 2 per cent solution is used against excessive sweating; a saturated solution in 50 per cent alcohol is employed for the prevention of bed sores. *Aluminum chloride,* which is more irritant, is used as deodorant and against localized sweating of feet and axillae, as a 25 per cent solution, applied at first twice, then once, a week (Stillians, 1916). *On mucous membranes* alum is applied as astringent in dilutions of ½ to 1 per cent for the conjunctiva and urethra, 1 to 5 per cent for gargling; but it is somewhat injurious to the teeth. Aluminum chloride has no advantage. Alum crystals may be used as styptic; exsiccated or "burnt" alum is somewhat caustic when applied in powder, mainly by abstracting water. *Protection against poliomyelitis infection,* by intranasal sprays of alum and other astringents, which gave promising results on monkeys, proved unreliable clinically (C. Armstrong, 1937; see further under Zinc Sulfate).

Colloidal aluminum hydroxide as antacid and protective in peptic ulcer, administered as a creamy suspension ("*Aluminum Hydroxide Gel*") corresponding to 16–32 Gm. of $Al(OH)_3$ daily, offers advantages over soluble alkalis in that its insolubility provides against excessive alkalinization; its solution by the gastric acid renders it astringent and antiseptic. The undissolved hydroxide also adsorbs intestinal bacteria, but is somewhat constipating.

Its administration decreases the secretion of total and free acid, especially in marked hyperacidity, without diminishing the response to histamine, even after the administration has been continued for several months. Symptomatic relief starts in a few days. No bad effects of any kind were observed. The absorption is insignificant, the urinary excretion amounting to less than 1 mg. per day (W. L. Adams, Einsel and Myers, 1936). It is also used by continuous intragastric drip (E. E. Woldman and Rowland, 1936). Ivy *et al.*, 1937, found prompt reduction of free acidity in response to the alcohol test. Havens, 1939, reported a case of fatal intestinal obstruction following intragastric drip of 2000 cc. of 5 per cent suspension daily for five days. In normal dogs, massive doses (120 cc.) produced no significant effects on the motility or tone of the stomach or pyloric antrum, or on the gastric evacuation time (J. P. Quigley *et al.*, 1939). It does not depress the gastric pouch secretion (W. L. Adams and Clark, 1944). The action is therefore chiefly that of buffering against the hyperchlorhydria of the ulcer patients. It interferes materially with the absorption of PO_4 by rats (S. Freeman, 1942). The administration of aluminum hydroxide with kaolin is reported to suppress coli growth in fecal cultures much more successfully than the kaolin alone (W. Smith, 1937).

Dried aluminum hydroxide can be prepared with different degrees of solubility, the truly amorphous being more soluble. The acid-soluble form is more effective for neutralizing gastric acidity; the acid-resistant form is more suited as adsorbent in the intestines (N. Mutch, 1946).

Fate.—Practically no absorption of aluminum occurs if its compounds are administered by mouth, either as soluble salts or as the hydroxide or carbonate, or as baking powder residues, which are largely dissolved by the acidity of the stomach. Virtually the entire amount is recovered from the feces, almost none from the urine, although parenterally injected aluminum is excreted by both channels; nor is the small normal aluminum content of the organs increased significantly even when the administration is continued over long periods, in man or dogs or rats.

The highest content, in the liver of rats, amounted to 0.161 mg. per 100 Gm., against the normal of 0.130 mg. (V. C. Myers and pupils, 1928). Older investigations led to contradictory results, due largely to inadequate analytical methods. These are discussed by Evelyth and Myers, 1932.

The *feces*, after oral administration, contain the aluminum largely as the insoluble *phosphate* (Schmidt and Hoagland, 1919). This prevents the absorption and utilization of the phosphate, and if the dosage is large and the phosphate income is small, in guinea pigs and rabbits, the blood phosphate may be lowered to 15 per cent of the normal, and urinary phosphate excretion may almost cease (G. L. Cox *et al.*, 1931). A form of rickets may be produced by this means, but it is practically unimportant unless the phosphate income is deficient. *With intravenous injection* of aluminum chloride, aluminum appears promptly in the urine, bile and feces; but a considerable proportion is retained (Evelyth and Myers, 1936).

Occurrence of Aluminum in the Tissues Normally and after Administration.—Although aluminum is but slightly absorbed, its wide distribution insures its continuous ingestion and universal presence in animal tissues, in concentrations of 0.06 to 0.22 mg. per 100 Gm. of fresh tissues, human, dog, rat and others. The addition of considerable quantities of various aluminum salts does not materially increase the concentration in the tissues, generally to less than 0.25 mg. per 100 Gm. Parenteral (intraperitoneal) administration of small amounts of aluminum chloride over three to six months causes more marked increase, especially in the liver and spleen, but concentration still does not exceed 1 mg. per 100 Gm. (V. C. Myers and pupils, 1928; Evelyth and Myers, 1936).

The concentration in the tissues of dogs, after oral administration, averages (mg. per 100 Gm. of fresh tissue): bile, 0.35; liver, 0.27; kidneys, 0.07; heart muscle, 0.12; brains, lungs, pancreas, urine, 0.10; spleen, 0.08; blood and bone, below 0.04. The liver of rats averages 0.08 mg. on Al-free diet; 0.14 on normal diet; 0.18 on Al-enriched diet; and 8.2 on intraperitoneal injection. E. W. Schwartze *et al.*, 1933, found the normal Al of guinea pigs to average less than 0.04 mg. per 100 Gm. Feeding large amounts of aluminum salts increased it to less than 0.1 mg. Wührer, 1934, also confirmed that feeding aluminum salts does not increase the aluminum of the organs.

The harmlessness of aluminum compounds on oral administration, even when prolonged (aside from local actions if concentrated solutions are swallowed, and the phosphate disturbance if large doses are given) is clearly established both by animal experiments and by clinical experience.

Rats fed for four generations with 2 mg. of alum daily did not show diminished growth or fertility or any other damage (Mull and Myers, 1928). McCollum *et al.*, 1929, similarly found that the addition of 0.06 per cent of aluminum compounds to the food caused no harmful effects on growth, reproduction or otherwise. Other investigators have arrived at the same conclusion, with few exceptions; and it is well to remember that many accidents may happen in prolonged experiments, so that absence of harm is more convincing than inconstant harm. Conversely, aluminum does not appear to be essential to growth; at least, no deficiency phenomena appear if the income in rats is reduced to 0.001 mg. per day (Hove *et al.*, 1938). *Clinically,* no deleterious effects were noted in patients who received 16 Gm. of the aluminum hydroxide daily for six months or longer (Einsel *et al.*, 1930).

In view of the harmlessness of aluminum, the question of the *ingestion of aluminum from cooking vessels* loses practical significance.

This has been the conclusion of various government boards after prolonged and exhaustive experiments on men and animals (J.A.M.A., *95:* 1849). Monies-Williams, 1935 (The British Ministry of Health, 1935; Report 78), concludes that distilled water takes up practically none of the metal; hard water and organic acids attack it slightly; alkalis markedly.

The question of *alum baking powder* has become similarly insignificant. The other types of baking powder, tartrate, phosphate and ammonia, are equally harmless under the conditions of their practical use (see below).

Rats fed for two generations with alum, tartrate and phosphate baking powders in double the proportion usually employed in baking showed no effects on growth or reproduction (W. C. Rose and Catherwood, 1929).

Powdered aluminum is nontoxic (Tocco and Mulas, 1935). Rabbits and guinea pigs exposed for many weeks to aluminum ("bronze") dust for six hours daily showed no pathologic conditions except respiratory catarrh when large quantities were inhaled (Ehrismann, 1939).

Powdered aluminum is being tried as a *prophylactic against silicosis.* It appears to be effective in animals (E. J. King *et al.*, 1945), but requires clinical confirmation (Report of Councils, J.A.M.A., *130:* 1223, 1946).

Intravenous injections of aluminum chloride, into rabbits, 2 or 3 mg. of Al per Kg., repeated daily, caused severe anemia, and changes in the white cells, kidneys and spleen (Seibert and Wells, 1929). Myers *et al.* did not find these effects in dogs, or with intraperitoneal injections in rats. Siem, 1886, described symptoms resembling those of subacute arsenic poisoning, appearing several days after subcutaneous injection. Apparently these have not been confirmed.

Baking powders are chemicals which serve as substitutes for yeast fermentation, aerating bread and pastry dough by evolving carbonic acid. They are, of course, altered in this process. The decomposition products are partly expelled by the heat of baking. The fixed residue is the part which could conceivably produce pharmacologic action.

The baking powders belong to four chemic types (Crampton, 1889):

1. **Cream of Tartar Powders.**—Mixture of acid potassium tartrate and sodium bicarbonate. Reaction: $KHC_4H_4O_6 + NaHCO_3 = KNaC_4H_4O_6 + CO_2 + H_2O$. Residuum: 11 Gm. of Rochelle Salts per loaf of bread.

2. **Phosphate Powders.**—Calcium superphosphate and sodium bicarbonate. Reaction: $CaH_4(PO)_4)_2 + 2NaHCO_3 = CaHPO_4 + Na_2HPO_4 + 2CO_2 + H_2O$. Soluble residuum: 3.5 Gm. of sodium phosphate per loaf of bread.

3. **Alum Powders.**—Alum (usually ammonic) and sodium bicarbonate. Reaction: $(NH_4)_2Al_2(SO_4)_4 + 6NaHCO_3 = Al_2(OH)_6 + 3Na_2SO_4 + (NH_4)_2SO_4 + 6CO_2$. Residuum, per loaf of bread: 1.3 Gm. of aluminum hydrate; 3.65 Gm. of sodium sulfate; 1.1 Gm. of ammonium sulfate. The aluminum hydrate is insoluble in water, but 10 to 22 per cent dissolves in the gastric juice and 10 per cent in the intestinal juice, regardless of acidity. Biscuits baked with various alum baking powders contained 15 to 92 mg. of Al per 100 Gm.; 0.4 to 14.6 mg. (2 to 20 per cent) of this was found in solution in the gastric contents of human subjects an hour after consuming the biscuits (V. C. Myers and Kilian, 1928). The addition of alum whitens pastry baked from inferior flour. This fraudulent use is prohibited in several countries.

4. **Ammonium Carbonate.**—Decomposed and volatilized as $NH_3 + CO_2$. Expelled so completely that it is inactive.

Some baking powders are mixtures of several of the above. They are often diluted with indifferent substances (starch, and so forth).

PREPARATIONS.—***Alum,** U.S.P.; Alumen; Potassium Alum; Aluminum Potassium Sulfate; $AlK(SO_4)_2 . 12 H_2O$; or Ammonium Alum, $AlNH_4(SO_4)_2 . 12 H_2O$; large colorless crystals, of strongly astringent taste, and without odor. Freely sol. in water (pot. alum, 1:7 ammonium alum, 1:5.2); practically insol. in alc.; freely sol. in glyc. *Incompatible* with alkalis, carbonates and lead salts. Dose, 0.3 to 0.6 Gm., 5 to 10 grains.—*Exsiccated Alum*, U.S.P. (*Burnt Alum*), is alum with 45 per cent of water (of crystallization) expelled.—*Aluminum Acetate Solution* (Burow's Solution), a clear colorless solution, contains about 5 per cent of aluminum acetate. Used as a mild astringent and antiseptic. A 1 per cent dilution is said to be antiseptic and a 5 per cent germicidal (Kuehl, 1913). For application to the skin it should be diluted five to fifteen times.

***Aluminum Hydroxide Gel,** U.S.P. (*Colloidal Aluminum Hydrate*); a white viscous, aqueous suspension equivalent to about 4 per cent of Al_2O_3, chiefly as hydrous oxide of aluminum. It may be flavored, and preserved by addition of sodium benzoate. *Dosage*, 4 to 8 cc. in water or milk every two to four hours, or by continuous drip through stomach tube. *Dried Aluminum Hydroxide Gel*, U.S.P., a white powder equivalent to not less than 50 per cent of Al_2O_3. Average dose, 0.6 Gm., 10 grains. *Aluminum Phosphate Gel*, N.N.R., an aqueous suspension of about 4 per cent of $AlPO_4$, has the same actions but does not interfere with phosphate absorption. Its dosage should be twice that of the Hydroxide Gel.

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RARE EARTH METALS

These resemble aluminum closely in pharmacological as in chemical properties. Their chlorides precipitate proteins and are therefore astringent and antiseptic. Their insoluble salts, such as the oxalates, are practically nontoxic by mouth, even in the enormous dose of 50 Gm. per dog (Dreyfuss and Wolf, 1905; Bachem; Hobert, 1907; Hoeber and Spaeth, 1914).

The *protein precipitation* depends on the salt concentration and on the *p*H. Properly buffered solutions of the chlorides of lanthanum, cerium and didymium do not precipitate (Oelkers, 1940).

Blood Coagulability and Liver Injury.—Intravenous injection of the chlorides (50 mg. per Kg.) lowers blood pressure and markedly lengthens the coagulation time of the blood for many hours, depending on the dose. The effect has been attributed to liver injury (central lobular necrosis, regeneration on withdrawal), but this is denied by Oelkers. The blood sugar level is lowered at the height of the action, and amino acids and urobilin appear in the urine. *In vitro*, coagulation is prevented by ¼ to ½ per cent of the salts. Hypodermic and oral administration are ineffective (Dyckerhoff *et al.*, 1936; Vincke and Oelkers, 1937; Fischler, 1938; Oelkers, 1940).

Cerium resembles aluminum. The insoluble Cerium Oxalate is employed against vomiting, especially in pregnancy (Simpson, 1854; Mills, 1876), but it is probably useless. It is nontoxic even in large doses.

Since cerium oxalate is not absorbed (Bachem, 1907), its action must be local and analogous to that of bismuth. Accordingly, Baehr and Wessler, 1909, found that it has no effect on central vomiting (apomorphine), but that large doses delay vomiting from local gastric irritation (ipecac). They also showed that central vomiting is not affected even by the soluble and absorbable cerium nitrate. The systemic effects correspond to those of thorium, but the metal is excreted exclusively by the feces. Cerium has been claimed to be beneficial in tuberculosis, but the evidence appears quite inconclusive (see Editorial, J.A.M.A., 1920, *75:* 247). Injection of neutral solution of cerium tartrate injures the heart, lowers the blood pressure and arrests respiration. Death occurs by pulmonary edema. Repeated sublethal doses do not seem to produce nephritis (Ozaki, 1919).

Cerium Oxalate is a mixture of the oxalates of cerium (about 40 per cent; Coblentz, 1910), didymium, lanthanum and other associated elements. Fine white or slightly pink powder, without odor or taste. Insol. in water. Dose, 0.05 to 0.5 Gm. as powder. *Cerium Nitrate* (soluble) has been substituted, in doses of 0.05 Gm. or less, but is irrational.

Beryllium is not used in therapy, but *industrial poisoning* has become important because of the increasing production and use, involving exposure to dust and fumes. It is extracted chiefly from a beryllium-aluminum silicate. In some processes this is fused with sodium silico-fluoride, and it is contended that systemic poisoning is due to fluoride, and that beryllium itself is not very toxic (F. Hyslop *et al.*, 1943).

Beryllium sulfate and especially the oxyfluoride (not the oxide) produce contact irritation with papulovesicular *dermatitis*. Inhalation of beryllium dusts or fumes causes irritation of the *respiratory tract*, the "berylliosis" of Fabroni, 1935, which may progress to fatal diffuse pneumonia or regress to complete recovery after removal from exposure. This is attributed to fluoride. Guinea pigs and rats do not show lung changes after exposure to industrial fumes (F. Hyslop *et al.*, 1943; H. S. Van Ordstrand *et al.*, 1945; review, L. T. Fairhall, 1945).

Oral administration to animals is practically nontoxic, and very little is absorbed. By peritoneal injection, the toxicity is less than that of zinc or magnesium. Hypodermically, it causes local edema and necrosis. Intravenous injections are toxic, with increased diuresis, bloody diarrhea and vomiting and disturbances of circulation, respiration and temperature. Beryllium salts inhibit the action of digestive ferments. Peculiar effects result in rabbits from intravenous injections of suspensions of beryllium silicate and oxide, twenty doses in six weeks: splenic atrophy; progressive hepatic cirrhosis; characteristic bone changes, cortical sclerosis, obliteration of marrow cavity, followed in seven months by *malignant osteosarcoma.* Beryllium is not demonstrable in the bones. These changes are not seen in other species or in man; nor do other chemicals induce them in rabbits (L. U. Gardner and Heslington, 1946). In amphibians, beryllium injections inhibit regeneration and cause perversions of *embryologic development* (A. E. Needham, 1941). Beryllium may take the place of magnesium in the growth of plants (Sestini, 1888).

Beryllium Rickets.—The feeding of beryllium carbonate or sulfate to rats results in disturbance of calcium deposition in bones, analogous to rickets, by lowering the plasma phosphate. This is attributable to the formation of the insoluble beryllium phosphate in the intestines. The mineral content of the bones is low and they do not contain detectable amounts of beryllium. This form of rickets is not prevented by cod liver oil or viosterol or ultraviolet irradiation (A. E. Sobel *et al.*, 1935).

Indium salts are slightly astringent, and hypodermic injections are somewhat irritant. Buffered with citrate and injected by the peritoneum, 2 mg. per Kg. in rabbits, 10 mg. per Kg. in rats, produce paralyses, localized convulsion and death with hemorrhages and degenerative changes in the liver, kidneys, ureter and lungs (C. P. McCord, Meek *et al.*, 1942). They have little or no effect on experimental syphilis in rabbits (von Oettingen; Steidle, 1933).

Gallium.—L. Schwarz and Sicke, 1928, reported irritation of the blood-forming organs. Levaditi *et al.* studied its distribution in the tissues of rabbits after intravenous and intramuscular injection of the tartrate. The kidneys generally had the highest concentration.

Yttrium was studied pharmacologically by Steidle and Ding, 1929. It is closely allied to cerium and aluminum.

Zirconium and Hafnium.—The effects of the oxychlorides on isolated organs were investigated by van Niekirk, 1937.

Lanthanum was studied as to local and general effects by Mancini, 1926; on smooth muscle by Bernardi, 1929.

Thorium.—The effects resemble those of aluminum. Nitrate of thorium is markedly astringent, precipitating proteins and coagulating blood. Injected hypodermically, it causes ulceration. The toxicity is slight. Very large doses are required to produce vomiting. It is not absorbed from the alimentary canal. The addition of sodium citrate prevents the coagulant action. When this solution is injected intravenously, it does not affect the circulation, or any other function, even with 0.25 Gm. per Kg. of dog. The thorium is excreted by the kidneys. It has no effect on the excised muscle or heart of frogs (Chace and Gies; Brown and Sollmann, 1907). The nitrate was tried for stimulating ulcers, but did not prove superior to alum. The oxalate and oxide are practically insoluble. Thorium salts cause swelling of frog erythrocytes and of sea urchin ova, even in hypertonic solutions of electrolytes or nonelectrolytes (Dorfman, 1932). The thorium-sodium citrate solution is opaque to x-rays, and was used for radiography (Burns, 1915). It has been displaced by other agents (sodium iodide or bromide, colloidal silver, iodized oil).

Radioactive Thorium Compounds.—Ordinary thorium gives off alpha rays and changes into mesothorium, whose chemical properties resemble those of radium and barium. It gives off beta rays and changes into radiothorium, and this, by giving off alpha rays, passes successively into thorium X and emanation. *Thorium X* is therefore the principal radioactive product. The distribution, excretion and effects are described by Plesch *et al.*, 1912. The actions and therapeutic uses are in all respects similar to those of radium. It is less efficient (Falta and Zehner, 1912; Gudzent, 1912).

Colloidal thorium dioxide as diagnostic roentgenographic agent (*Thorotrast*) was introduced for intravenous injection to outline the vascular system, locally, and especially to outline the liver and spleen because it is picked up from its intravascular injection by the reticulo-endothelium of these organs (E. Randerath and Schlesinger, 1931). It was also used for ventriculograms of the brain and for mammograms of the lacteal duct system. It gives good pictures, and most patients have shown no ill effects for months or years. The thorium oxide that remains behind is a grave potential hazard, however, for it acts not only as a foreign body, but the clinical intravenous dose of 75 cc. emits gamma radiation equivalent to 1.37 microgram of radium; 2 micrograms of the latter have produced symptoms of radium poisoning (Taft, 1937). In addition, it gives off alpha rays which are considered 10,000 times more dangerous than gamma radiation. The absence of reaction, even after some years, does not preclude later trouble, as ten to fifteen years may elapse before gross changes can be demonstrated in radium poisoning. Microscopic changes have already been reported. Intravascular injection leads to extensive destruction of the arterial elastic tissue. The thorotrast from *intraperitoneal injection* is slowly absorbed, remaining practically unchanged in six months. Local degenerative changes are at first similar to those of other mild irritants, but after eight to twelve weeks they correspond to roentgen irradiation of the peritoneum (L. Efskin, 1941).

Fate.—Soon after the intravenous injection, the thorium oxide particles are taken up phagocytically by monocytes, neutrophils and especially by the reticulo-endothelial cells. Here it persists for years, new cells taking up the thorium from the dying cells (R. Pomeranz, 1934). Traces are also found in the parenchymal cells of the liver, suprarenal cortex and ovaries (Irwin, 1932; Wen and Jung, 1934). It is excreted slowly, chiefly as thorium X, and can be demonstrated in the liver, spleen, bone marrow and reticulo-endothelial cells generally for over a month after relatively small doses (Barkan, 1940). In a patient who died after several days, half of the injected thorium was found in the liver, large amounts also in the spleen, and traces in the long bones (Taft, 1937).

Considerable remained in the tissues of two patients who had received 75 cc. of thorotrast six or seven years previously. When 2 cc. were injected by vein into rabbits, the blood contained a negligible amount after five hours. After four months, the radioactivity of the organs of the sacrificed animals was twenty times higher in the spleen, and four times higher in the bone marrow, than in the liver, per Gram of tissue; bone shafts contained relatively little (W. Stenstrom, 1941). In a dog killed five years after the injection, practically none had been eliminated (Naegeli and Lauche, 1936).

Histologic Changes.—Intense degeneration was observed, especially in the liver and spleen of animals, but they practically recovered in two or three months (Shute and Davis, 1933). Two human autopsies showed proliferative reactions in the connective tissue and radioactivity of the liver, five months after the injections (Fleming and Chase, 1936). On the other hand, Rigler *et al.*, 1935, with three and a half years of experience on 175 patients, report little or no hepatic damage demonstrable during life or post mortem (the latter on thirty-five cases). C. W. McClure *et al.*, 1944, insist that no harmful effects have been reported from its clinical use for the fourteen years since its introduction. No carcinogenic activity has been reported clinically or experimentally after intravenous injection; but larger subcutaneous or intraperitoneal injections into rats and mice were followed by subcutaneous or peritoneal sarcoma (Roussy *et al.*, 1935; Selbie, 1936). This has not been demonstrated clinically (W. M. Yater and Whitmore, 1938).

Injections into the cerebrospinal fluid spread widely, so that it is found in the meninges of the cerebral cortex after lumbar injection (Freeman and Schoenfeldt, 1936). Severe Nissl changes in the cerebral cortex were reported after spinal injections in animals (Koshimizu, 1935).

Injections into the lacteal duct system have repeatedly given rise to severe foreign body reactions, granulomatous changes and necrosis, necessitating amputation of the breast (Reis and Mesirow, 1938; Romano and McFetridge, 1938).

RADIUM

Thorium, radium and uranium undergo atomic decay into a series of new elements (emanation, and so on). This decay is accompanied by the generation of rays which produce irritant or destructive effects which are utilized in the radiation treatment of localized malignant tumors. Their internal use was tried against various conditions, especially rheumatic and arteriosclerotic, without much success. It is no longer justified, in view of the serious chronic progressive osteosarcomatous changes of radium poisoning, due to the continued radiation from the retained radium, which is deposited similarly to lead, particularly in the bones. The chemical properties of radium, and probably also its direct pharmacological actions, resemble those of barium.

Because of its chemic reactivity, radium cannot be kept in the metallic state. It is marketed in the form of its salts, especially the soluble bromide or chloride, and the insoluble sulfate and carbonate. It is generally mixed with more or less of the corresponding barium salts and is sold on the basis of its radium content.

Disintegration of Radium.—This proceeds at such a rate that half of the element will be transformed (*i. e.*, a "half period") in about seventeen hundred years. It goes through a number of successive products. The first is formed by giving off alpha rays and consists in a gas niton, or radium "emanation" or "radon," with a half period of not quite four days; this emits weak alpha rays, changing to radium A (induced radioactivity), and this, with successive losses, of alpha, beta and gamma rays, in proportions characteristic for each compound, goes through radium B, C (three varieties), D, E and F.

Disintegration of Other Radioactive Metals.—Radium itself is formed by the disintegration of uranium, through the stages of: Uranium = Uranium X = Ionium = Radium. *Thorium* takes the course: *Thorium* $-\ \alpha =$ Mesothorium; $-\ \beta =$ Radiothorium; $-\ \alpha =$ Thorium X; $-\ \alpha =$ Emanation; $-\ \alpha =$ Thor. A; $-\ \beta =$ Thor. B; $-\ \alpha =$ Thor. C; $-\ \alpha =$?

Radium emanation or "*radon*" consists of the element "niton," a heavy, inert gas of the argon group. It is liberated continuously from slightly acidulated solutions of radium salts, and may be collected, purified, liquefied and dispensed in capillary tubes applied to, or implanted in, the tissues, in place of radium. It produces the same effects, but because of its rapid decomposition its action diminishes quickly and stops automatically in a few days; the action of radium endures indefinitely and practically undiminished. The emanation may also be dissolved in water, for internal use. *Thorium emanation* loses its activity within a few minutes.

Radium Deposit.—Substances exposed to radium become coated with active deposits, consisting of all the degradation products. The "half period" of this "induced radioactivity" is an hour. Such deposits on lead foil may be used for superficial application; or exposed sodium chloride may be used for making solutions for intravenous injection.

Varieties of Rays.—The rays emitted by the disintegration of the metals are of three kinds, differing in their nature, their velocity, penetration and ionizing power: Alpha rays are positively charged helium atoms; the beta rays are negatively charged electrons, identical with the cathode rays; the gamma rays are electromagnetic vibrations in the ether, a variety of the roentgen rays, but of shorter wave length and deeper penetration. The three varieties of rays produce qualitatively similar *effects*, differing mainly in degree and in the power of penetration. These two properties vary inversely: *i. e.*, the actions of the alpha rays are superficial and most intense; those of the hard gamma rays are the deepest and most moderate. The effects on living tissues progress, according to the duration of the exposure, from stimulation to inflammatory reaction and destruction. The susceptibility of the tissues varies in degree, being in general proportional to the growth rate, and being additive to already exciting irritation, inflammation or necrotic degeneration. Tumors are therefore more susceptible than normal tissue; rapidly growing tumors more than benign; sarcoma, especially lymphosarcoma, more than carcinoma. Lymphoid tissue, the sexual glands and capillary endothelium are also very susceptible. The *bones* store relatively large quantities of radium, thorium and polonium, and become thin and brittle, due to osteitis and rarefaction, with increased liability to infection. The deposits are mobilized by parathyroid hormone, but not by viosterol.

Topical Application.—One of the most important fields in radiotherapy is the treatment of tumors. Specialized training and experience are required to decide the advisability of the treatment, and to select and apply the rays so as to secure the desired degree of action on the tumor tissue, with the minimum of harm to the normal tissues. Ovaries and testicles are especially susceptible to permanent injury.

Fate of Radium.—Soluble radium salts, injected or taken by mouth, are excreted rather slowly, mainly by the large and small intestines, somewhat by the urine, none by the liver or skin (E. Smith and Bellingham, 1912; Brill and Zehner, 1912). The storage is mainly in the liver and spleen. The insoluble radium sulfate is very little absorbed, but its emanations are carried through the tissues. With hypodermic injection of radium chloride into rats, half to two-thirds is excreted in a week, the remainder much more slowly. In chronic administration about 25 per cent is retained, 99 per cent of this in the bones (H. E. Thomas and Bruner, 1933). The *emanation* has a high lipoid coefficient and is distributed in the organs in proportion to its solubility (Knaffl-Lenz, 1912). When injected intravenously into rabbits, 95 per cent was exhaled within five minutes (R. R. D. Milligan and Rogers, 1928). With *inhalation*, the amount in the blood increased with the time of exposure. The excretion is rapid, especially by the expired air, and partly by the urine. It is completed in about four hours.

Systemic effects are important chiefly from the standpoint of chronic poisoning. *Acute and subacute effects* have been imperfectly studied.

Inhalation of large amounts of emanation leads to dyspnea and depression (but not true narcosis), terminating in death. The autopsy shows widespread hyperemia, with histologic changes in the brain cells, and to a less degree in other central nerve cells (Knaffl-Lenz, 1912; Poulsson, 1908).

Excised Heart.—Zwaardemaker, 1916, reported that the potassium of Ringer's fluid may be replaced by equiradioactive quantities of any of the radioactive metals, and that therefore the action of potassium in aiding automatic contractions is due to its radioactivity. Further work is needed to confirm this theory.

Chronic Industrial Radium Poisoning.—Martland, in 1925, reported the development of necrosis of the jaw and progressive anemia in girls who had been engaged a year or longer in painting luminous watch dials and had conveyed small quantities of radium-containing paint to the mouth with the brush. The patients either died of general sepsis or developed rapidly growing osteogenic sarcoma in various bones (Martland, 1931), perhaps in response to the irritation of bacterial invasion of the necrotic tissue. Considerable quantities of active radium were isolated from the bones of those who died (Gettler). Miners of radioactive ores are said to show high incidence of primary lung carcinoma. Martland called attention to the danger of therapeutic ingestion of radioactive waters; those containing only emanation are probably excreted and harmless (J. P. Leake, 1932, review). Neutrophile leukopenia is an early and constant feature of overexposure. Different individuals vary in sensitivity. The more sensitive develop early lymphocytosis. Eosinophilia is also a frequent early occurrence. Restoration of the leukocyte count requires variations of more than four weeks (Goodfellow, 1935). The risk of dial painting has since been practically abolished by mechanical processes. Removal of the absorbed radium from the bones has been attempted by viosterol and decalcification regimen (F. B. Flinn); but Cravert and Schlundt, 1935, failed to mobilize a significant amount from four radioactive girls during three months of the treatment with viosterol and parathyroid extract.

Experimental chronic radium poisoning has resulted in osteogenic sarcoma and the other changes characteristic of clinical chronic poisoning, in rabbits (M. Rosenthal and Grace, 1936; also with mesothorium; F. R. Sabin *et al.*, 1932) and in rats (H. E. Thomas and Bruner, 1933; R. D. Evans *et al.*, 1944). Direct introduction of radium into the liver produced sarcomas and carcinomas in rats, mice and guinea pigs (Biltris, 1933). Intravenous injection into dogs caused chronic renal insufficiency, without hypertension and without changes in other organs (L. J. Adams *et al.*, 1933). *Dental changes* on oral administration of radium sulfate were studied on rabbits by M. Rosenthal, 1937. He found the radium stored in the teeth as well as in the alveolar bone, producing profound changes in the entire morphologic picture of the tooth, enamel organ and periodontal structures.

Radioactive isotopes of various elements are being used to localize radiation in the tissues for which they have special affinity. They avoid the radiation sickness, which is attributed to massive tissue destruction (P. F. Hahn and Sheppard, 1946). *Radioactive sodium acid phosphate* is reported to produce marked improvement in chronic lymphatic and myelogenous leukemia, polycythemia vera and lymphosarcoma. The results in Hodgkin's disease are doubtful. *Radioactive strontium* is being investigated for neoplasms of bone, *radioactive iodine* against hyperthyroidism (R. V. A. Low-Beer *et al.*, 1942).

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SILVER

The inorganic silver salts, especially the nitrate, are used to produce astringent, caustic and antiseptic effects. They form resistant precipitates with proteins, so that their local action is easily controlled. The toxicity for higher animals is low, and the antiseptic efficiency is high. In the tissues, silver surpasses mercury, since the protein compounds of silver as well as the colloidal oxides and metallic silver liberate a small quantity of silver ions. These may be used directly when antiseptic action without irritation is desired. Silver is not absorbable in sufficient quantity from the alimentary canal to produce systemic actions. Because of its precipitation by proteins and chloride, even large doses of silver nitrate rarely cause serious poisoning. Long-continued use of any silver preparation results in blackish discoloration of the skin (argyrism) by the deposition of silver particles, probably organic. Traces must therefore be absorbed.

Local Astringent and Caustic Action.—Silver nitrate acts as astringent, irritant or caustic, according to the strength and duration of its application. The surface turns white, then gradually gray and black by the reduction to metallic silver and oxide. The precipitation permits easy control of its action. The nitrate, fused into pencils ("lunar caustic"), sometimes "mitigated" with potassium nitrate, is applied in substance for the removal of warts and the stimulation of ulcers and granulations. The pencils should be moistened before use. Painting with 10 or 20 per cent solution is used for the same purpose. The concentrated solutions are said to be less painful than the more dilute. A 1 per cent solution is instilled in the conjunctival sac for the prevention of ophthalmia neonatorum. Dilute solutions of 1/100 to ½ per cent (see tabulation) are employed as astringent and antiseptic in acute and chronic catarrhal inflammations of mucous membranes, especially against gonorrhea and congestion of the deep urethra. The mucous membrane should be cleansed before the silver is applied. The solutions must be made with distilled water. The caustic and astringent action may be stopped with sodium chloride. The antiseptic action of silver nitrate extends deeply, since it forms easily soluble double salts of silver albuminates and sodium chloride in the tissues (Lubinsku, 1914).

In ophthalmia neonatorum, silver nitrate must be used with caution, or cauterization of the cornea and blindness may result, especially if the applications are repeated. For prophylaxis a single drop of 1 per cent silver nitrate which is marketed in wax capsules should be placed in the conjunctival sac, at birth, after cleansing the eyelids. This should be followed in a few minutes by normal saline, to arrest the irritant action. In treatment, where the applications are repeated, the strength should never be above 1 per cent, and generally not over 0.5 per cent. Indeed, 0.5 per cent applied every four hours is more effective also for prophylaxis, and does not produce inflammation (A. B. Bruner).

The efficiency of the silver nitrate prophylaxis is not so well established as is commonly assumed. When it was introduced by Credé, he reported that it had reduced the ophthalmia incidence in his clinic from 10.8 to 0.2 per cent. Later statistics, however, show about 2 per cent. Crede's method originally included vaginal douching with 2 per cent phenol, which may have had the larger share in his results. Lehrfeld, 1935, recommends superficial sterilization of the birth canal and thorough flushing of the eyes with boric solution, followed by 0.5 per cent silver nitrate, repeated on three successive days, and continuing the boric flushing for two weeks.

Smoking.—Painting the posterior pharynx with 10 per cent silver nitrate, or rinsing the mouth with 0.5 per cent after meals, gives rise to a disagreeable irritating taste when smoking is attempted.

Pills of silver nitrate, 10 to 20 mg., ⅙ to ⅓ grain (made with kaolin and petrolatum), were used in gastric ulcer, and the like. There is probably a slight local action before the silver is precipitated, and after it is dissolved by protein. The oxide, 0.03 to 0.1 Gm., was similarly employed. The gastric use of silver compounds is not advisable, since their efficiency is slight and they carry considerable risk of argyrism.

Amomniacal silver nitrate is applied locally to arrest the progress of *dental caries* (Howe); the precipitated silver sterilizes the dentin. It penetrates slowly, but in the course of a month the precipitate is carried into the pulp (J. A. Zander and Burrill, 1943).

Silver Stains.—The stains produced locally by the direct application of silver salts are quite distinct from argyrism and wear off spontaneously. Recent and superficial stains are easily removed by rubbing with a crystal of potassium iodide, or painting with a 10 per cent solution, which is allowed to remain for several hours. One application usually suffices (Wilkinson, 1932). Full strength "chlorox," followed by scrubbing with soap, is also effective. Effective but less safe are 10 per cent potassium cyanide and 10 per cent mercuric chloride in 10 per cent ammonium chloride (Mankiewicz, 1916).

Colloidal Silver Preparations.—The antiseptic action of silver nitrate is complicated by irritation, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds, but when they are not necessary they are undesirable. Colloidal silver preparations avoid these effects, as most of their silver is not ionized and does not precipitate chloride or proteins. Their antiseptic action is also due to the small amount of silver ions, which may be present in free form, or adsorbed by the colloids (Pilcher and Sollmann, 1924; Dreser, 1917; Neergaard, 1923). Their concentration is low and their precipitant and corrosive actions are mitigated by the presence of proteins, which serve as protective colloids and as demulcents (Kolthoff and Tomicek, 1925). The major part of the silver which is in colloidal form appears to be inactive, and does not increase the antiseptic action, even on prolonged contact (Pilcher and Sollmann, 1924). The activity of these preparations is therefore independent of their silver content, but is determined by the ion concentration which varies for the different compounds.

A striking correspondence exists between the ionization (as judged by the inhibition of the growth of yeast) and the concentrations that have been selected, for instance, for conjunctivitis, by the empirical experience of the clinics. The "oligodynamic" action of metallic silver is also due to the liberation of silver ions (D. Abel, 1920).

The *mechanism* of these effects is analogous to the late action of silver nitrate. This probably acts in two stages: (1) the immediate, irritant and germicidal effects produced by the direct application of the free silver ions; and (2) the later, milder antiseptic effects produced by the re-solution and ionization of the silver-protein compounds formed in the first stage. If this second stage alone is desired (*i. e.*, antisepsis without irritation), the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation. The absence of coagulation membrane would facilitate their access to the cells; they form more concentrated solutions than are likely to be formed from the re-solution of the silver precipitates in situ; the colloidal aggregates are likely to be smaller and therefore more reactive; and because of the absence of irritation, they are likely to be more frequently applied and would therefore secure a more continuous action.

Composition and Classification.—Metallic silver and insoluble compounds of silver such as the oxide, the halogen salts (iodide, chloride, and so on) and silver protein precipitates may be brought into "colloidal solution"; *i. e.*, if they are sufficiently finely divided, they become miscible with water, so that they apparently go into solution, actually as permanent suspensions of the insoluble substance in a state of ultramicroscopic particles. The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide, or some protein-silver precipitate in an excess of denatured protein, and drying in vacuum. This results in substances that dissolve freely although somewhat slowly in water, yielding brown-colored "colloid solutions," which consist of probably indefinite mixtures of metallic silver, silver oxide, and various silver-protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced. Although there are gradations, the products on the market fall into a small number of fairly definite groups: the members of each group are practically equivalent therapeutically, although they possess minor peculiarities, due mainly to the nature of the proteins used as protective colloids. The adjectives "strong" and "mild" refer to the therapeutic action, *i. e.*, to the silver ions, and not to the total silver content, which happens generally to be in the inverse order.

Strong protein silver (*protargol type*) contains a lower percentage of silver (7 to 8.5 per cent), but in solutions this becomes largely ionized; so that they have the strongest germicidal action, but are also distinctly irritant. The irritant action of protargol is estimated as about 1/10 that of silver nitrate (Neisser), confirming that practically all the silver is ionized. The strong silver proteins are therapeutically between silver nitrate and mild silver protein.

Protargol is said to be prepared by precipitating a "peptone" (albumose) solution with silver nitrate, or with moist silver oxide; dissolving the silver peptonate in an excess of protalbumose; and drying in vacuo (Fraenkel). Another preparation (Protargentum) is said to be prepared by the action of silver nitrate on gelatin, in the presence of an alkali, precipitation by alcohol and drying.

Mild protein silver (*argyrol type*) contains 19 to 30 per cent of silver, of which only a small fraction is ionized, together with alkali proteins which confer demulcent properties. They are therefore not irritant, but rather soothing. To this type belong argyrol, cargentos, silvol, solargentum, and the like. They are prepared by the action of alkali protein on moist silver oxide, and drying in vacuum.

Collargol appears to be a variety of the mild silver-protein type, containing a larger proportion of colloidal silver (78 per cent), said to be prepared by reducing silver nitrate with ferric citrate (Bechhold, p. 366), and also stabilized by alkali albumin. It was intended mainly for intravenous injection, to provoke the "colloidal reaction" which is sometimes useful in infections. It has been suggested that the proteins play the major part in this reaction (Bottner, 1921; W. Lutz, 1921).

Electrically Dispersed Silver.—Metallic silver may be brought into colloidal solution by forming an arc between silver electrodes under water. These solutions, however, are dilute and unstable, and gradually form silver oxide and ionic silver.

Colloidal Silver Haloid Salts.—Silver iodide and chloride may also be obtained as colloidal suspensions. These do not differ in principle from the other colloidal preparations; some are more, some less, ionized.

Interference of Chlorides and Proteins.—Silver chloride is insoluble and therefore ionizable only to a limited extent, so that in the presence of chlorides the silver ion concentration does not reach the irritant and astringent level, but the concentration may suffice for a limited degree of antiseptic action. Proteins increase the dispersion and therefore the solubility of the silver chloride (Stas; Glovczynski, 1914).

Changes on Standing.—Watery solutions of the colloidal silver compounds tend to alter on standing, the direction of the changes being the reverse in the strong and mild silver protein: with the *protargol type*, the silver ions decrease slowly, by about one-fifth in a month, by one-half in a year. Their therapeutic activity would be correspondingly decreased, but this would have little therapeutic importance. With the *argyrol type*, the silver ions increase, by slow ionization of the colloidal silver, and the solutions therefore become more efficient but also more irritant. Tish process is sufficient to be clinically important; the silver ions increase by one-third to one-half in a week, and by one-half to three times in a month and onward (Sollmann and Pilcher, 1924).

Therapeutic Uses.—The colloidal silver compounds are used as antiseptics on mucous membranes. The strong silver protein group is the most effective, but is distinctly irritant and stimulant. The compounds of the mild silver protein group act largely as mucilaginous demulcents and protectives, and as detergents, by dislodging pus.

Dosage and Administration.—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong silver protein; from 5 to 50 per cent for mild silver protein, and from 0.02 to 1 per cent for collargol. These are applied every two to four hours. The details are shown in the tabulation. Solutions should be recently prepared, and should be protected against light. Stains on linen are removed by 1:1000 solution of mercuric chloride. The usual concentrations for special purposes are shown in the tabulation.

	Strong Protein Silver Per Cent	Mild Protein Silver Per Cent	Silver Nitrate Per Cent
Eye:			
Conjunctivitis, simple, purulent or gonorrheal	2 to 10	Solution, 25 Ointment, 10	0.2 to 2 (see text)
Prophylaxis against ophthalmia neonatorum	2 to 10	25	0.5 to 2 (see text)
Corneal ulcers		50	
Nose and throat	0.5 to 10	Spray, 10 to 20 Swab, 25 to 50	2 to 10
Ulcers			0.1 to 10
Gonorrhea:			
Injections—Prophylactic	2	10	
Acute	¼ to 1	3 to 10	
Urethral irrigation	1:2,000 to 1:1,000	1:1,000	1:10,000 to 1:2,000
Cystitis		20 to 50 (5 cc.) or 10 to 25 (30 cc. left in the bladder)	1:5,000
Gynecologic practice:			
Solutions	2 to 10	25 (tampons of solution in glycerin)	
Tampons	5		
Ointments	5		
Suppositories	5	Suppositories, 20 (0.3 Gm. or 5 grains)	
Rectal:			
Irrigation	0.1	0.1 to 1	
Injection	2	10	
Suppositories	5 to 10	20 (0.13 Gm. or 2 grains)	

Pyelography started with colloidal silver solutions (Völcker and Lichtenberg, 1906). They have been displaced by the iodized compounds.

Intravenous injection of colloidal silver (collargol) was used to produce "nonspecific reactions" for the treatment of septicemic conditions. This form of therapy is now rarely employed, and other agents are safer than silver. The injected silver is taken up by the reticulo-endothelial cells, which are thereby "neutralized," so that they cannot take up other particulate matter. The blood cholesterol is markedly decreased (Goebel and Gnoinski, 1927). Repeated injections of nonlethal doses into dogs produce hyperplasia of the bone marrow, never aplasia. Large single doses cause pulmonary congestion and edema, with death in twelve hours (Shouse and Whipple, 1931).

Toxicology.—Silver nitrate to 0.01 or 0.1 Gm. by mouth produces no symptoms. Swallowing pieces of the pencils up to 2½ Gm. is also often harmless. Larger quantities cause acute gastritis. The actions are purely local. Death has occurred in a few hours to a few days from 2 to 30 Gm.; 10 Gm. are generally fatal, but 30 Gm. have been survived. The *treatment* would be by sodium chloride and demulcents.

Symptoms start with burning in the throat and epigastrium, followed by violent abdominal pain; black vomitus; severe salivation; diarrhea may or may not be present; the patient goes into severe shock. Death occurs by convulsions (which may set in early with large doses), or in coma. The lungs appear normal (Hill and Pillsbury, 1939).

Subacute silver poisoning has been reported apparently in only one case resulting from silver nitrate applications over two months to an extensive burn. The patient developed argyrism of the mucosa, severe diarrhea and convulsions, and died (Olshausen, quoted by Gerschun, 1894).

Systemic actions are not seen in man, but may be produced in animals by the injection of nonprecipitant silver solutions (AgCl in sodium thiosulfate, Gaehtgens, 1890; colloid AgCl or AgI, Gros, 1912). The actions are mainly on the central nervous system, with paralyses and spasms, beginning in the lower extremities; disturbances of respiration; and fall of blood pressure; sometimes diarrhea. The secretion of bronchial mucus is greatly increased, probably by injury to the epithelium, and may lead to asphyxia. Death usually occurs promptly, by paralysis of respiration; the diaphragm is paralyzed before the other respiratory muscles. The heart is but little affected and may beat after death. In frogs, the paralysis is preceded by convulsions (Ball, 1865; Jacobj, 1877; Gaehtgens). *Chronic systemic poisoning* shows changes in the blood corpuscles; disturbances of metabolism; cloudy swelling of the heart and skeletal muscle; and fatty degeneration of the liver and kidney (Bogoslovski).

The *therapeutic use of silver in nervous diseases* (insanity, epilepsy, and so forth) was a survival of medieval concepts based on its dedication to the moon, and the supposed connection of the latter with lunacy. Although silver cannot be absorbed in amounts sufficient to have any action, it has been tried again and again against all forms of nervous disease with uniformly negative results.

Argyrism (argyria, argyrosis) consists in a permanent bluish black discoloration of the skin, ashen gray in lighter cases, involving also the mucosae (conjunctiva) and internal organs. It is due to the deposition of a silver compound and develops gradually when silver in any form enters the tissues, by direct injection, or by continued application to mucous surfaces or open wounds or by prolonged oral ingestion. It is permanent and incurable and should be prevented by judicious use. The blueness is first recognizable in the areas exposed to light; in most cases in the face, often on the conjunctiva, sometimes in the distal margin of the lunule of the finger nails; its appearance here should lead to the immediate discontinuance of the use of silver (I. S. Wright, 1933). The buccal mucosa often shows discoloration, sometimes other mucosae; a "gum line" is present in about 10 per cent. About half the reported cases were due to silver nitrate, but many cases have been reported from the routine use of colloidal silver preparations, especially by the laity as prophylaxis against colds, generally in children and young people (Gaul and Staud, 1935; Olson, 1917). It has also followed the injection of silver arsphenamine. The oral administration of silver was formerly a frequent cause (Blumberg and Carey, 1934). It has been produced by the application of silver-containing hair dyes. The intensity of the discoloration depends on the quantity of silver and of exposure to solar and especially to ultraviolet radiation (Zacks, 1933).

Historical.—Argyrism is said to have been first reported by Angelus Sala in 1647. It was extensively studied by Frommann, 1859; Riemer, 1876; and Gerschun, 1894; industrial argyria by J. M. Harker and Hunter, 1935. A comprehensive monograph "Argyria" was published by Hill and Pillsbury, 1939 (Williams and Wilkins Co.). The term "argyrosis" is sometimes restricted to the eye.

The *pigment* consists of opaque granules, easily soluble in potassium cyanide, but difficultly in concentrated nitric acid, so that they are not metallic silver or silver oxide, as was formerly believed (B. Riemer, 1876). In the skin, they are located in the collagen and especially in the elastic fibers of the corium, immediately under the epithelium, and about the sweat and sebaceous glands. The dark-field method of Hoffmann and Berek shows that its distribution in the skin is much more extensive than it appeared to be (Habermann, 1924).

The first appearance of argyria is usually in the eye, in the conjunctiva and eyelids, especially the lower, and also in the cornea, chiefly in Descemet's membrane. It can also be produced there from long-continued local application (Bruchker and Knapova, 1929; W. Dieter, 1929). Argyria can be induced in experimental animals by oral as well as by parenteral administration, but rarely appears to involve the skin, perhaps because the fur protects against light. It is seen especially in the mucosae and internal organs. Silver may be deposited in practically all structures, excepting perhaps nerve, muscle and epithelial cells, but the quantitative differences between organs are marked. Connective tissue and blood vessels are universally involved; relatively rich are the skin, renal glomeruli, choroid plexus, mesenteric glands, thyroid (Hill and Pillsbury, 1939). The silver may be outside or inside. The pigment appears first in the reticulo-endothelial cells and in the leukocytes, and is distributed by these through the body, where it occurs as intra- and extracellular granules (Gerschun), apparently in the cement substance and membrana propria, probably most abundantly in the kidneys at the junction of the cortex and pyramids, and in the liver. Silver determinations in argyrosis patients always show the highest percentage in the kidneys; Frommann, 1860, for instance, found 61 mg. per 100 Gm. of kidney, 40 mg. per cent for liver. In persons not exposed to silver the concentration does not exceed 1 mg. per 100 Gm. of dry tissue (Sheldon *et al.*, 1933). The deposited silver causes no symptoms. *Other metals* that may cause somewhat similar discoloration are bismuth, arsenic and gold. Kobert, 1893, emphasized analogies with siderosis; but Gerschun, 1896, pointed out significant differences.

Absorption of silver occurs from all mucous and serous membranes more rapidly with silver chloride and nitrate than with the colloidal compounds. Unbroken skin does not absorb enough to produce argyria; nor is this likely to result from the brief use of silver as caustic. Absorption may occur from the respiratory tract, but chiefly from the upper small intestines. The form in which it is absorbed and transported is presumably chloride or proteinate. In the blood it exists chiefly in the plasma, some in the phagocytes, none in the red cells (H. Blumberg and Carey, 1934; B. Minz, 1930). A patient with generalized argyria *excreted* less than 2 mg. of silver per week in the feces, none in the urine (N. L. Kent and McCance, 1941). The *time of treatment* before argyria appears is usually two or three years; rarely less than six weeks. *The total amount of silver* administered orally is probably never less than 6 Gm. With argyria after intravenous injection of silver arsphenamine, the average amount was 16 Gm., containing 2.3 Gm. of silver; it occurred rarely with half of this dosage.

Argyrism *persists* indefinitely or disappears slowly. Crispin, 1914, and Olson, 1916, believed that recovery is hastened by methenamine. Stillians and Lawless, 1928, reported some success with multiple endermic injections of a solutionc ontaining 1 per cent of potassium ferricyanide and 6 per cent sodium thiosulfate. Mercuric chloride decolorizes the granules *in vitro*, but not *in situ*.

PREPARATIONS.—***Silver Nitrate,** U.S.P. (Argenti Nitras; Lunar Caustic); $AgNO_3$. Colorless crystalline tablets, becoming gray to black on exposure to light in the presence of organic matter. Odorless; metallic taste. Freely sol. in water (1:0.4), sol. in alc. (1:30). *Incompatible* with chlorides, bromides, iodides; carbonates and hydroxides; organic drugs and reducing agents. *Toughened Silver Nitrate,* U.S.P. (Silver Nitrate Pencils; Stick Caustic), contains about 5 per cent of silver chloride to toughen the mass. *Silver Picrate,* N.N.R., is used against vaginal infections by Trichomonas, Monilia and gonococci, as watery solution, powder (1 per cent in Kaolin), suppositories or jelly (Corbit *et al.*, 1941). ***Strong Silver Protein** (Protargol) contains not less than 7.5 per cent and not more than 8.5 per cent of silver. A brown, odorless powder, usually somewhat hygroscopic; freely sol. in water. Slightly but distinctly irritant; not precipitated by chlorides, which, however, interfere with the action. Applied as a 0.1 to 10 per cent solution. Solutions are best made by sprinkling the powder on cold water, without stirring. Solutions of strong protein silver should be freshly prepared and dispensed in amber-colored bottles. Products of this type are: Proganol-Heyden, Protargentum-Squibb, and Protargol-Winthrop. ***Mild Silver Protein,** U.S.P. (Argyrol), contains not less than 19 per cent and not more than 23 per cent of silver Dark brown or almost black scales or granules; frequently hygroscopic; freely sol. in water. Not precipitated by or incompatible with chlorides. Applied as 10 to 40 per cent solution in water. Solutions of mild silver protein should be freshly prepared and dispensed in amber-colored bottles. Products of this type are: Argyn-Abbott, Argyrol-Barnes, Cargentos-Mulford, Silvol-Parke Davis, Solargentum-Squibb, Vargol-Heyden. *Silver Iodide,* freshly precipitated, was recommended by Siter and Uhle, 1905. Colloid silver iodide has been used intravenously, similarly to collargol, producing leukocytosis, and so forth (Voigt and Corinth, 1919). A colloidal silver odide preparation is marketed as "*Neo-Silvol*"; a coloidal silver chloride as "*Lunosol.*"

◆

GOLD

Gold salts are readily reduced to metal, which is poorly absorbed. Intravenous injections, especially of gold and sodium thiosulfate, and sometimes intramuscular injection of oil suspensions of soluble salts, produce rather striking reactions, perhaps by flocculation of the reduced gold. They are used with marked success in lupus erythematosus and certain other skin diseases; with more variable success in rheumatoid arthritis; with rather disappointing results in pulmonary tuberculosis and in asthma; and without success in leprosy. They are fairly effective against syphilis, but inferior to arsphenamine, bismuth and mercury. The oral administration (sometimes only pretended) as a "tonic" and "alterative," and for the cure of dipsomania, is a mystification, like the "potable gold" of the alchemists which was to be the elixir of life and youth—to the charlatan. The parenteral administration, and especially the intravenous, is a rather dangerous procedure.

The *mechanism of the therapeutic action and of the toxic reaction* is not known, but may be connected with the flocculation of the reduced gold. This would be analogous to the "nonspecific protein reactions," involving the reticulo-endothelial system.

Therapeutic Efficiency in Lupus Erythematosus.—The good results reported by Schamberg and Wright, 1927, have been confirmed by many others. Marked improvement or entire healing of the lesion occurs in about two-thirds of the patients, but sometimes with recurrence.

Rheumatoid Arthritis.—Long-continued intramuscular or intravenous injections of soluble gold salts produce gradual improvement in about ⅓ to ½ of patients, especially in early cases, apparently arresting the inflammatory process. Other joint diseases are not improved. The mode of action is not known. Many patients relapse. Familiarity with the treatment and extreme care in its application are essential. Serious toxic effects may develop at any time during the administration (see below). This should therefore be used only if the diagnosis is clear, and the disease has lasted more than three months, so that it is not likely to improve spontaneously (B. I. Comroe, 1945; E. F. Hartung, 1943). Many physicians have abandoned its use (Hench, 1946).

The improvement usually does not begin until the injections have been continued for one to three months. It starts with relief of the pain in the joints, then the joint swellings soften and subside and the general health improves. In about a third of the patients the arrest of the disease persists over a year.

Several workers have found that gold preparations benefit experimental proliferative arthritis in *mice*. The effect is not bacteriostatic, nor does it correlate with the toxicity (A. B. Sabin and Warren, 1940).

Pulmonary Tuberculosis.—Gold cyanide had been recommended against tuberculosis and scrofula by Chrestien, 1811. It fell into disuse, but the observation of Robert Koch, 1890, that gold salts inhibit the growth of tuberculosis bacilli in cultures, prompted further trials. Bruck and Glueck, 1913, claimed successful results from intravenous injection of gold-potassium cyanide (especially when combined with tuberculin!) in lupus and in syphilis, but DeWitt, 1918, found gold salts unsuccessful in experimental tuberculosis of guinea pigs. Indeed, they tended to shorten life, through hemorrhage and hyperemia. Nevertheless, Mollgaard, 1924, claimed beneficial results from the intravenous injection of gold and sodium thiosulfate, under the name of "Sanocrysin." The results in pulmonary tuberculosis again proved disappointing (Editorial J.A.M.A., 1926, *86:* 487; Miyagawa, Jap. Res. Com., 1927).

Syphilis.—Gold treatment was tried early, and Legrand of Amiens in 1836 wrote a book upon the subject, in which he ranked gold with mercury; but since it was administered orally, it must have been quite ineffective. Positive results by the intravenous injection of gold and sodium thiosulfate were obtained in rabbit syphilis by Levaditi, and confirmed clinically by Fournier and Mollaret, and by Jeanselme and Burnier. Judged by the effect on the Wassermann test, it is generally less effective than arsphenamine or bismuth, but may succeed when these have failed.

Clinical Toxicity.—Erythema, pruritus, urticaria and rashes occur frequently, generally some hours after injection. Serious reactions are infrequent with care and restricted dosage, but they may be fatal. They include renal irritation, exfoliative dermatitis, ulcerative enteritis, leukopenia, thrombopenia, agranulocytosis, aplastic anemia. G. S. Mirick, 1940, reviews the eighteen cases of agranulocytosis reported to that time as following gold therapy. Basophilic granulations, probably regenerative, were observed in 94 per cent of rheumatic patients treated with gold (Hulst, 1937). The literature is reviewed by Driver and Weller, 1931; the fatal cases by Fatzer, 1935.

The *toxic effects in animals* resemble those of arsenic (Schultz, 1892). Oral administration of gold chloride to dogs produces emesis. With hypodermic or intravenous injection, the acute toxicity of the thiosulfate is rather low; indeed, there may be no immediate symptoms with doses that prove fatal after two weeks with characteristic changes in the erythrocytes, violent diarrhea, and especially degeneration and necrosis of the renal epithelium which is the cause of death. Therapeutic doses produce some renal congestion and slight degeneration (Orestano, 1933; Kallo, 1934). Repeated injection of nearly fatal amounts produces tolerance up to twice the ordinary lethal dose by greater resistance of the regenerated renal epithelium (R. Cortell and Richards, 1942). Theobromine decreases the acute toxicity of sodium gold thiomalate; theophylline has no significant effect (K. I. Melville, 1944).

Dimercaptopropanol (BAL) is proving successful in various gold toxicities: acute (A. Cohen *et al.*, 1947); dermatitis (C. Ragan and Boots, 1947); and granulocytopenia (L. M. Lockie *et al.*, 1947). It hastens the urinary elimination of the gold (Ragan and Boots).

Fate.—Gold administered as the thiosulfate is fairly rapidly but incompletely *absorbed* after oral administration to rabbits (Orestano, 1933). The colloidal preparations are absorbed more slowly than the crystalline from intramuscular injections (W. D. Block *et al.*, 1941). With *clinical administration* of the thiosulfate or thiomalate, 75 to 80 per cent of each injection is retained indefinitely; the remainder is excreted chiefly by the urine, four times more than by the feces. Gold can be demonstrated in the blood plasma for long periods, up to ten months, after discontinuing the injections, the time increasing with the dosage (R. H. Freyberg *et al.*, 1943; B. I. Comroe, 1945). The highest concentration of the *retained gold* is in the kidney, then usually the liver, the other organs being more variable. In the blood, it is practically all in the serum, and only traces are in the corpuscles. Deposition in the skin leads to "chrysiasis." A patient who died of ulcerative enteritis two weeks after the last of a series of intravenous injections of gold and sodium thiosulfate yielded the following quantities of gold, mg. per 100 Gm. of moist tissue: spleen, 3.4; kidneys, 2.5; liver, 0.6; colon, 0.2; lung, 0.1 (N. L. Anderson and Palmer, 1940). *Colloidal gold*, injected intravenously, is retained practically entirely in the liver (95 per cent), somewhat in the spleen, and very little in the kidneys and lungs (Lomholt, 1926; Heubner, 1929; Henius and Weiler, 1929; Kurosu, 1927). With intramuscular injections of colloidal gold or gold sulfide into rats, the liver contained almost ten times more gold, the kidneys only a sixth, than when gold and sodium thiosulfate was injected. Almost half of the administered thiosulfate gold was excreted by the urine, only a thirtieth of the colloidal (W. D. Block and Buchanan, 1941).

Normal Presence of Gold.—This is said to be in amounts almost comparable to the common metals, 0.03 to 1 mg. per cent in most food materials, with normal daily excretion in man amounting to 0.1 mg. in the urine and 1 mg. in the feces (R. Berg, 1928.)

"Chrysiasis," permanent skin discoloration by deposited gold, analogous to argyria, may result from repeated injections of small doses (Hansborg, 1928), but generally only after large doses; indeed, generalized pigmentation is rare. It is normally preceded by erythema, in contrast to argyria (Cascos, 1936). Blonde women are reported more susceptible (Curtis and Conte, 1936). *Injection* of gold compounds outside the vein produces a local greenish-blue discoloration (Schamberg, 1928).

Gold appears to be eliminated into the *skin and hair*, as is arsenic. None is found there normally, in human or rabbits, but it appears in the skin after eight to sixty days of oral administration of the thiosulfate, and in the hair after forty-five days (Casazza, 1934; Glingani, 1934).

Administration and Dosage.—*Gold Sodium Thiosulfate* ("Sanocrysin"), $Na_3Au(S_2O_3)_2.2H_2O$, contains approximately 37.4 per cent of gold. It occurs as white crystals freely soluble in water. It is marketed in ampuls of 10, 25, 50 and 100 mg. The solution is colorless and neutral or faintly alkaline. It should not be administered unless liver, kidney and other serious organic disease has been excluded. The dosage should be started with 5 mg., intravenously, in 2 to 5 cc. of sterile distilled water. Injections are repeated at weekly intervals, increasing by 5 mg. at each injection, provided no untoward reactions occur, to the maximum of 50 mg. for women, 75 mg. for men, to a total of 500 to 1000 mg. for the course, and six to eight weeks should intervene before a second course is undertaken. The patients should be closely watched, and a differential white count taken weekly. In mild reactions the dosage is reduced; with severe reactions it must be discontinued. Extreme hypersensitivity is likely to exist in patients with the disseminated type of lupus erythematosus, and if gold is used at all in them it must be with extreme caution and probably with not more than half of the usual dosage. *Gold Sodium Thiomalate* (*Myoschrysin*) is used in rheumatoid arthritis with somewhat lower dosage (B. I. Comroe, 1945).

Gold and Sodium Chloride (Auri et Sodii Chloridum) is the salt usually employed orally. Dose, 5 mg., $\frac{1}{12}$ grain. It is a mixture of equal parts of anhydrous gold chloride ($AuCl_3$) and anhydrous sodium chloride. Orange-yellow powder, odorless, saline and metallic taste; deliquescent. Very sol. in water.

PLATINUM

The actions on animals are similar to those of gold (Kebler, 1878; Cohnstein, 1892).

RHODIUM

Sodium and rhodium chloride hypodermically or, better, intravenously is effective against experimental syphilis and frambesia of rabbits, with a therapeutic index of 1:25 to 30. It causes considerable local irritation. Rhodium chloride, $RhCl_3$, is more toxic (Jahnel, 1937).

COPPER

Cupric sulfate irritates the nerve endings in the stomach which gives rise to the vomiting reflex, and thus has a rather specific emetic action. It is also used on mucous membranes as an astringent and caustic. Copper ions catalyze a number of reactions, and minute quantities of copper are essential in the metabolism of plants and animals; but a little more is toxic. It has a relatively high toxicity for fungi, protozoa and algae, and has been employed for the purification of water, but it is not a reliable bactericide. Its absorption is limited and its toxicity to animals is therefore low, but large doses may be fatal. The ingestion of the small quantities normally present in food promotes the conversion of iron into hemoglobin in nutritional anemia. It is itself a constituent of the blood pigment of mollusks and crustaceans.

Astringent and Caustic Action.—Solid copper sulfate is used as a mild escharotic against granulations and trachoma. The everted lid is lightly touched with the copper crystal or pencil, and then rinsed with water. The pencils are made by fusing 1 part of potassium alum with 2 parts of copper sulfate. Solutions of 0.1 to 3 per cent may be employed as stimulant astringents in conjunctivitis, urethritis and vaginitis, but have no particular advantage over silver.

Antiseptic Action and Use in Water Purification.—Copper may be used to purify water from contamination with algae. The traces of copper remaining in the water are probably harmless. It is fairly effective against bacteria of the coli group. Its use against typhoid contamination seems to be unreliable (Clarke and Gage, 1906). Thomas, 1915, describes its use for the disinfection of swimming pools.

Copper sulfate is effective as *anthelmintic* against various gastro-intestinal parasites of the sheep, a drench of 1.5 per cent solution being administered every three weeks. No ill effects were noted (Reitz, 1935).

Emetic Action.—Copper sulfate is effective and prompt, with short nausea. It is irritating, however; and should it not be effective there is some danger of poisoning, and it must be removed by lavage. It is therefore not to be recommended, except in phosphorus poisoning, in which it oxidizes the phosphorus and coats the globules with a layer of metallic copper. The emetic dosage is 0.5 Gm., in a single dose; or three doses (if necessary) of 0.25 Gm. each, fifteen minutes apart. It should be dissolved in a glass of water.

Acute Toxic Actions.—Large doses (20 Gm.) of soluble copper salts produce hemorrhagic gastro-enteritis, nephritis, collapse and coma.

Copper Metabolism.—Small quantities of copper are probably indispensable. The *copper content* of a human adult is 100 to 150 mg.; the *daily turnover* is 2 to 2.5 mg. This is the copper content of the ordinary diet, and the amount of the total *excretion* (Tompsett, 1934; T. P. Chou and Adolph, 1935).

In *American children of preschool age*, the daily intake was found to range from 0.07 to 0.11 mg. per Kg. of body weight. This gave a retention of 0.012 to 0.048 mg. per Kg. of body weight, so that 0.1 mg. per Kg.

appears to furnish an adequate supply for growth (A. L. Daniels and Wright, 1934). In young women on self-chosen diets, the daily intake averaged 2.65 mg. with average retention of 0.85 mg. A larger proportion was retained when the intake was increased (R. M. Leverton and Binkley, 1944).

Normal Copper in Food.—Traces of copper, as of other metals such as manganese and zinc, occur universally in plants and animals (Flinn and Inouye, 1929), and therefore in food. Larger quantities are found in organic combination in the liver, fat and other organs of *cephalopods* (octopus) crustaceans, snails, mussels and insects, but only small amounts in vertebrates (K. Okamoto *et al.*, 1938).

The *copper content of food* ranges from 0.1 mg. per Kg. for fresh celery to 44 mg. in fresh calves' liver (Lindow, Elvehjem and Peterson, 1929). Cow's *milk* normally contains 0.12 to 0.18 mg., average 0.15 mg., per liter, with rather small differences between herds. It is not increased by feeding copper to five times the normal income (Elvehjem, Steenbock and Hart, 1929), but it may be considerably increased by contact with copper vessels. The copper of human milk runs somewhat higher, 0.21 to 0.28 mg. per liter.

The **absorption** of copper from the alimentary tract is limited, so that its administration does not increase the urinary excretion above the normal, which is less than 1 mg. daily. The *skin* can absorb some copper from the oleate (C. L. Vogt and Buckhardt). The *urinary excretion of copper* is about 0.25 mg. daily in adults, ranging between 0.08 and 0.7 mg. (Rabinowitch, 1933; Tompsett, 1934), and is approximately the same in dogs (A. Ross and Rabinowitch, 1935). It is not affected by the income. The *fecal excretion* is ten or twenty times greater, varying with the food income.

Retention.—The *increase with growth and with copper administration* is illustrated by the rat data of Lindow, Peterson and Steenbock, 1929: the total copper content increased to forty times, from 0.011 mg. at birth to 0.44 mg. at seven to eight months. The content at birth was not raised by increasing the copper intake of the mother. Addition of copper to the food increased the copper content of the body by two or three times. The increase was greatest in the liver, to twenty times; only to 1.6 times in the bones; the copper of the blood increased only to 1.6 times, from 0.055 mg. to 0.082 mg. per cent. Of the copper added to the food, about 98 per cent was eliminated by the feces, but the content of the urine was increased by five times. The copper content returned to the normal level in four or five weeks after the administration was discontinued.

The *copper content of organs* is highest in the liver, which shows the largest increase when copper is administered. Human liver averages 0.75 mg. per 100 Gm. Its content follows a characteristic curve during life, the kidney content does not (Brückmann and Zondek, 1939). The spleen, kidneys and lungs average about 0.25 mg. per 100 Gm. (Gerlach, 1935; Tompsett, 1935). Fetal liver is especially rich in copper (H. Ramage, 1934). Gerlach did not find the liver concentration significantly changed in hepatic cirrhosis, diabetes, tuberculosis or blood diseases, but K. Okamoto *et al.*, 1938, describe its occurrence in the cells of nonpigmented and atrophic cirrhosed liver. Copper is always present in human *bile* (Judd and Dry, 1935). Human *blood serum* contains normally 0.062 to 0.124 mg. per 100 cc. (Kraft, 1928). Human *whole blood* contains 0.185 to 0.229 mg. per 100 cc., so that the copper is fairly evenly distributed between the corpuscles and plasma (Tompsett, 1934; Sachs, Levine and Fabian, 1935; children, Currado, 1933). *Fetal blood* contains 0.195 to 0.235 mg. per 100 cc. at five to six weeks of gestation, 0.073 to 0.082 at term, 0.100 to 0.176 in older infants. The content is generally higher in anemias (whole blood, 0.70 to 1.33 mg., average 0.98, Bence *et al.*, 1936; serum, Sachs *et al.*, 1935). The normal blood and tissue copper appears to be in loose nondialyzable combination with proteins, in the serum with the albumin. It is dissociated by acid (R. Boyden and Potter, 1938).

Hemocyanin, the blue blood pigment of mollusks and crustaceans, is a copper compound, probably molecular, differing somewhat in the different classes of animals. That of limulus contains 0.173 per cent of copper and 17.3 per cent of nitrogen (Redfield *et al.*, 1928).

Hematinic Action.—The traces of copper normally present in the food, or their addition to artificial diets, aid greatly as supplements to iron in the formation of hemoglobin in young animals (E. B. Hart and Steenbock, 1928) and in nutritional anemia, in all species studied, including birds and man (J. Waddell, Steenbock and Hart, 1929; dogs, A. R. Maase *et al.*, 1944). V. C. Myers *et al.*, 1931, reported that most other metals produce similar effects, although they generally require larger doses. It is doubtful whether this action of copper is of therapeutic importance, for extreme precautions are necessary to produce experimental copper deficiency, so that a spontaneous deficiency appears improbable (A. H. Smith, 1933). The subject is discussed under Iron (see Index; review, M. O. Schultze, 1940).

Copper Deficiency.—The rigorous exclusion of copper from the diet of rats is fatal in a few weeks (McHargue). A regional disease of cattle and goats, characterized by diarrhea, loss of weight and loss of black color, was found by Sjollema, 1938, to be associated with low copper content of the blood, liver, spleen and hair, and improved when copper was administered.

Fur and Skin Color.—The fur and underlying skin of black or hooded rats changes gradually to a silvery gray when they are fed an exclusive milk diet poor in copper, and returns promptly to the darker color when copper is added (H. S. Keil and Nelson, 1931); but not on the addition of iron and other inorganic elements, or of vitamins. Similar changes occur in black cats and rabbits (Gorter, 1935): The black fur and the skin under it have a somewhat higher copper content (about one-fourth) than the unpigmented areas (Cunningham, 1931; Sarata, 1935), and it is plausible that copper acts as a local catalyst in the formation of the pigment in the skin. The *feather pigment* of certain birds contains copper, probably as part of the pigment molecule.

Catalytic functions of copper are especially important for the oxidation of *sulfhydry compounds* such as cysteine (S. M. Rosenthal and Voegthir, 1933). In *plants* it is the prosthetic group of ascorbic acid oxidase (J. F. McCarthy *et al.*, 1938) and of phenol oxidase (F. Kubowitz, 1938).

Adventitious copper in foods and drink is probably harmless in the quantities in which it is likely to be present.

Copper may be introduced into foods by *insecticide sprays*, such as Paris Green or Bordeaux Mixture, but these owe their toxicity to the arsenic, not the copper. However, the U.S. Food Administration has set 30 mg. per Kg. of food as the permissible limit of extraneous copper. Copper may enter the *water supply* in the copper sulfate treatment for algae. The U. S. Treasury Department has set a limit of 0.2 mg. per liter for potable waters, which is surely on the safe side. *Copper cooking vessels or piping* does not impart significant quantities to water or food. Copper is sometimes used to give a bright green color to canned *vegetables*, especially peas and beans. These contain 25 to 120 mg. per Kg. The copper enters into a firm compound with the chlorophyl. Older vegetables, not so rich in chlorophyl, contain it in much looser combinations with proteins. The chlorophyl compound produces no effects of any kind, even when continued for long periods in quantities corresponding to 12 to 15 mg. of Cu per day, the maximum amount which would be taken in food. The use of copper with young green vegetables would therefore be harmless (J. H. Long, 1912), and it is doubtful whether harm could result even from the looser compound in old vegetables. *Prolonged* administration of copper sulfate up to 0.5 Gm. per day has been shown to be devoid of bad effects (Du Moulin). It is true that these were not continued indefinitely.

Inhalation of copper dust may cause changes in the gums of exposed workers, probably by local action. Rabbits subjected to copper dust half an hour daily for two to eight weeks showed no toxic effects or pathological changes, although the copper concentration of the liver rose to thirteen times the normal average (Remy and Zimmermann, 1931).

Hepatic cirrhosis and hemochromatosis ("gin-drinker's liver") was attributed by Mallory, 1926, to the long-continued consumption of copper, as contamination of alcohol, the latter potentiating the metal. The causal connection is not proved, and is improbable. Experimental evidence has been contradictory, and the clinical occurrence of increased copper concentration in the liver is not constant and need not be significant (Gerlach, 1935).

Addition of copper sulfate to the diet of rats receiving *p-dimethylaminobenzene* delays the production of liver tumors by 25 to 50 per cent, although it does not prevent them (G. R. Sharpless, 1946).

Intravenous injection of copper salts lowers blood pressure, doubtless largely by flocculation. In rabbits, intravenous injection of 10 to 20 mg. of copper acetate or cadmium salts (but not other metals) *induces ovulation* (so also do metrazol and picrotoxin). This effect probably consists in stimulation of the hypophysis, for it is prevented by transsection of the hypophyseal stalk (C. M. Brooks *et al.*, 1940; C. W. Emmens, 1940). Intravenous injection of 0.1 cc. of 1 per cent copper acetate induces pseudopregnancy in adult estrous rats, as does also pituitary extract. The copper probably acts through the posterior pituitary (A. Drury and Bradbury, 1942). The copper ovulation in rabbits is inhibited by progesterone (M. H. Friedman, 1941). *Excised* skeletal and cardiac muscle are depressed by copper salts. Autonomic responses are altered as by other precipitants. Epinephrine, for instance, is rendered stimulant to the intestines and uterus (Hazama, 1925).

Colloidal copper has been injected intravenously for tumors, without real success. Its distribution in the organs is similar to that of copper salts (Corper, 1914). It has repeatedly caused serious inflammation, necrosis and gangrene at the site of injection. *Colloidal copper sulfide* was studied by Lo Cascio, 1930, with oral, hypodermic and intravenous administration.

Ethylenethiocarbonate derivatives of copper were tried by Dixon and Hoyle, 1929, against experimental tuberculosis in guinea pigs and rabbits, but the results were not promising.

PREPARATIONS.—***Cupric Sulfate, U.S.P.** (Blue Vitriol, Bluestone); $CuSO_4.5H_2O$; large, deep blue crystals; odorless; metallic taste. Freely sol. in water (1:3); slightly sol. in alc. (1:500); freely sol. in glyc. (1:2.8). *Incompatible* with fixed alkalis and carbonates. Dose, emetic, 0.3 Gm., 5 grains. *Cupric Citrate*, U.S.P.; slightly soluble in water. *Cupric Citrate Ointment*, U.S.P., 8 per cent.

ZINC

The local actions of the *soluble zinc salts* resemble those of copper, but are less potent. Zinc sulfate is employed as emetic, and locally as astringent and antiseptic. Other soluble zinc salts are also used locally. The acetate is milder; the chloride is escharotic. The insoluble zinc oxide and stearate are used externally as protectives, similarly to bismuth. There are no systemic effects under therapeutic conditions, but traces of zinc are indispensable in nutrition. Inhalation of fumes of zinc oxide causes "metal fume fever."

Insoluble zinc compounds, the oxide, carbonate and "*calamine*" (a native zinc carbonate), are employed extensively in dermatology as mildly antiseptic and astringent, protective and sedative applications in inflammatory skin diseases and on superficial wounds. They may be applied dry or as ointment, alone or mixed with boric acid, bismuth subnitrate, starch or phenol. The calamine is often used as a 5 to 10 per cent aqueous suspension, or as the *Calamine Lotion* or *Calamine Liniment*. *Zinc stearate* forms a light fluffy dusting powder which is not adhesive and does not cake; but it has the serious disadvantage that fatal pneumonia results if a considerable quantity of the light dust is inhaled. Such accidents are not infrequent when infants play with the containers. The latter should be devised so that they cannot spill considerable quantities of the powder.

Zinc undecylenate is among the most effective preventive agents against fungus skin infections, such as athletes' foot. It may be applied as powder, 20 per cent in talcum, with 2 per cent of undecenylic acid; or as ointment of 5 per cent of the acid and 18 per cent of the zinc salt (H. C. Shaw *et al.*, 1945).

Zinc sulfate as emetic acts like copper sulfate, and is generally preferred, being nearly as efficient and less irritating. The short nausea, slight depression and absence of harmful irritation make it particularly suitable in gastric disturbance from overeating. One to 2 Gm., 15 to 30 grains, may be given in a glass of water.

Astringent and Antiseptic Action.—Zinc sulfate or acetate is used in conjunctivitis, particularly that caused by the Morax-Axenfeld bacillus, which it arrests promptly by inhibiting the bacterial proteolytic enzyme. It is also employed in chronic gonorrheal urethritis and other catarrhal conditions. The strength of solution for collyria is 0.1 to 1 per cent; for urethral injections, 0.5 to 4 per cent. The phenolsulfonate has no advantage.

Poliomyelitic Prophylaxis.—Spraying the nasal mucosa of monkeys with 1 per cent zinc sulfate solution, as with other astringents, affords considerable protection against experimental inoculation with poliomyelitis virus (Armstrong and Harrison, 1935). It appears to be totally ineffective in man (Armstrong, 1937), perhaps because of the difficulty of effective application (E. W. Schultz and Gebhardt, 1937); but it is doubtful whether the virus naturally enters by the nasal mucosa.

Zinc chloride as escharotic is used as the Liquor Zinci Chloridi on granulations, ulcers, and the like. It has been extensively exploited as *disinfectant* and overestimated in proprietary preparations. MacClintic, 1905, found 1:200 to 1:500 a poor germicide and feeble antiseptic, though a fair deodorant. Injection of 5 per cent zinc chloride solution into the testis of fowl produces *teratomas* of rapid growth, exceeding 200 Gm. in two or three months, which continue to grow after transplantation (Anissimova, 1939).

Zinc in Food.—Birckner, 1919, showed that traces of zinc are common in many foods (review, D. M. Hegsted *et al.*, 1945). Milk contains about 4 mg. per liter, hen eggs about 1 mg. per egg. However, spectographic data indicate that the zinc content of food is almost 40 per cent lower than the published data (Scoular, 1939). Zinc is almost invariably present in oysters from the Atlantic Ocean. It is probably always associated with copper, but the two metals do not occur in uniform ratio (Hiltner and Wichmann, 1919).

The excretion of zinc varies with the income, as little is retained. In dogs it amounts normally to 5 to 25 mg. per day. Nearly all of this, 94 to over 99 per cent, is in the feces, and most of this was not absorbed. The *normal urinary* excretion in dogs is 0.13 to 0.49 mg. per day. The urinary excretion was but little increased by feeding zinc oxide to dogs and rats and cats for three to fifty-three weeks and soluble zinc salts to rats. A part is excreted by the bile. The excretion returns to the normal level two weeks after the administration is discontinued. Practically none of the administered zinc is retained (K. R. Drinker *et al.*, 1927; normal children, Scoular, 1939). If radioactive zinc is injected *by vein* it disappears rapidly from the blood plasma and appears early in the red corpuscles, increasing during the 170 hours of observation. The maximal deposition is in the liver, which after two hours contains about a third of the injected amount. Considerable is excreted by the pancreatic juice and by the duodenal secretion, practically none by the bile. About a third of the injected dosage is eliminated by the feces in one or two weeks, 2 per cent or less by the urine (M. L. Montgomery *et al.*, 1943; G. E. Sheline *et al.*, 1943; human, R. A. McCance and Widdowson, 1942).

The *total zinc* of mice on normal diet averages 0.434 mg. (Bertrand *et al.*, 1935), which would correspond to about 1 Gm. in a human adult. The *distribution* of the normal zinc shows striking peculiarities. Its concentration is relatively high in the *pancreas*, where it probably forms a part of the *insulin* molecule. It is a constituent of carbonic anhydrase (0.3 per cent) (Keilin and Mann, 1940), and all the zinc in the red blood corpuscles is bound to this enzyme (Hove, Elvehjem and Hart, 1940). It is also high (80 to 450 ppm) in the *epidermal structures*, hair, finger and toe nails and feathers. It is about the same in pigmented and unpigmented hair (Eggleton, 1938).

Deficiency phenomena have been studied on rats and mice with synthetic diets low in zinc, but adequate in other factors. These show nutritional disturbance due to marked interference with intestinal absorption, especially of nitrogen; retardation of growth and subnormal body weight; and roughing of the fur, alopecia and eczema. The *skin* changes involve abnormal keratinization, thickening of connective tissue, and loss of hair follicles. There is vascularization and leukocytic infiltration of the *cornea*, similar to riboflavin deficiency. The *esophagus* is also affected (R. H. Follis *et al.*, 1941) The growth deficiency can be counteracted by transplantation of anterior pituitary. The deficiency symptoms occur if the daily zinc income of the rat is less than 40 gamma; with 22 gamma, the growth rate is retarded by half. All the phenomena are corrected by *adding* zinc (Hubbell and Mendel, 1927; Hove *et al.*, 1938). More severe withdrawal causes paraplegia and death of mice in fourteen to twenty-three days, of rats in two or three months (H. G. Day and McCollum, 1940). The average total zinc content falls to about half the normal (Bertrand and Bhattackerjee, 1934, 1935). In rats, Hove *et al.*, 1938, found the tissue Zn but little decreased by a zinc-deficient diet; the greatest reductions were in the bones, teeth and blood. The significance of zinc for living organisms was reviewed by K. R. Drinker and Collier, 1926. Zinc deficiency is not of clinical importance, as the ordinary income is adequate. Scoular, 1939, concludes that the diet of the preschool child should include 0.31 mg. per Kg. daily.

The **oral toxicity** of zinc compounds is low. Zinc oxide or soluble zinc salts in quantities considerably larger than those that could be introduced in food, *f. i.*, from zinc containers, appear to be innocuous. They cause no apparent symptoms or pathologic changes even when administered daily for a year to dogs and cats, or to rats for several generations, nor is the zinc content of the organs increased (Heller and Burke, 1927; K. R. Drinker *et al.*, 1927; C. K. Drinker and Fairhall, 1933). In drinking water, 30 to 40 mg. per liter is considered safe (D. M. Hegsted, 1945).

No effects result when 0.1 per cent of zinc carbonate is added to the diet of rats; but 0.5 per cent causes anemia and disturbed reproduction; and 1 per cent prevents reproduction (W. R. Sutton and Nelson, 1937). Dornick, 1938, reported food poisoning in a group of people who ate apples cooked in a galvanized iron kettle, so that apples contained 83 mg. of zinc per 100 cc., and the vomitus 17 mg. per 100 cc. The bacteriologic findings were negative, but other metals (cadmium?) were not excluded. *Chronic industrial zinc* poisoning has been reported for workers in galvanizing plants (McCord and Friedlander, 1926) and in processes employing zinc chloride (du Bray, 1937). The symptoms were chiefly gastro-intestinal (nausea and vomiting), but also hypochromic anemia. They were probably due to more toxic metals, Pb, Cd, As and Sb, which are common in zinc ores (Batchelor *et al.*, 1926).

Feeding zinc to rats produces hypochromic anemia and deficient growth (S. E. Smith and Larson, 1946).

Systemic effects of *intravenous injection* of soluble zinc salts are mainly paralytic. Consciousness is lost, but the motor areas are not involved. The blood pressure falls rapidly, probably by flocculation of the plasma protein. Blood coagulation is retarded for an hour after the injection of 5 to 50 mg. per Kg. in rabbits, probably by increase of antithrombin (Melon, 1926). Rabbits develop glycosuria and generally albuminuria after intravenous injection of zinc malate, also after larger doses hypodermically. The quantity of urine is either diminished or unchanged, rarely increased (Salant and Wise, 1918).

The movements of *excised intestines* are depressed by very dilute solutions, abolished by medium concentrations (Salant and Mitchell, 1916). Long-continued ingestion of zinc salts by cats results in fibrotic changes in the acinar portion of the *pancreas*, without affecting the islets (K. R. Drinker *et al.*, 1927). Zinc oxide has been used as a *nervous sedative*, in epilepsy, and so forth, but is useless.

Metal fume fever or "*Brass founder's ague*" is produced by the inhalation of the finely divided zinc oxide formed in the combustion of the metal, even of pure zinc (Lehmann, 1910), and of the vapors and fumes of all heavy metals and their oxides: brass, Cd, Pb, Hg, Hn, As, Sb, Cu, Sn, Ni, Ag, Fe; and also by magnesium oxide (Koelsch, 1923). After exposure of several minutes or hours, depending on the susceptibility and ventilation, there is slight irritation of the throat; but the main symptoms occur later, often after the patient has been in the air for some hours, and they are aggravated by cooling of the body. The attack resembles a malarial chill, which may last some hours, with ordinary febrile symptoms—lassitude, headache, nausea, muscle cramps and joint pains, constricting sensation over lungs, leukocytosis. The attack ends in twelve to twenty-four hours, with perspiration and rapid recovery. It is often diagnosed as influenza or pneumonia, and in animals severe exposure may result in bronchopneumonia (reviews, C. K. Drinker, 1937; R. R. Sayers, 1938).

The phenomena are presumably analogous to those of the inhalation of zinc stearate. Lehmann attributes the symptoms to the absorption of the remains of the respiratory cells destroyed by the zinc. The zinc oxide formed by burning the metal in air appears as branching needles under the electron microscope (L. C. Martin, 1942). This may partly account for the injury. The hypodermic injection of zinc salts also produces fever (Kisokalt, 1912); but so do other irritants.

Repeated exposure to zinc fumes leads to tolerance, which is soon lost if there is no further exposure. It may result in chronic lesions of the respiratory, digestive, excretory and nervous systems (Hayhurst, 1913; Chrometzka, 1936); but C. K. Drinker, 1937, asserts that these are not caused by pure zinc, but by contamination with more toxic metals.

Welding fumes may produce toxic effects by oxidation of the coating metal; zinc if galvanized, lead if painted. The oxides of the iron core are not toxic (B. D. Tebbens and Drinker, 1941; H. K. Sessions, 1944).

PREPARATIONS.—**Soluble Zinc Salts.**—***Zinc Sulfate,** U.S.P. (Zinci Sulfas; White Vitriol); $ZnSO_4 \cdot 7H_2O$. Small colorless crystals, odorless, metallic taste. Very sol. in water (1:0.6), with acid reaction. *Incompatible* with alkalis, carbonates, sodium borate. Dose, as emetic, 1 Gm., 15 grains. *Zinc Acetate*, U.S.P.; $Zn(C_2H_3O_2)_2 \cdot 2H_2O$; soft white plates; faintly acetous odor; astringent metallic taste. Freely sol. in water (1:2.5) with neutral reaction. *Zinc Chloride*, U.S.P.; $ZnCl_2$. White granular powder or porcelain-like masses or in pencils; highly caustic. Very sol. in water (1:0.5).

Insoluble Zinc Compounds—***Zinc Oxide,** U.S.P., (Zinci Oxidum); ZnO; a very fine amorphous, white or yellowish-white powder, without odor or taste. Practically insol. in water or alc. ***Zinc Oxide Ointment,** U.S.P. (Zinc Ointment), contains 20 per cent in white ointment, with 7 per cent of wool fat. *Lassar's Paste*, used in eczema, contains zinc oxide, 1 part; starch, 1 part; white petrolat., 2 parts. *Calamine*, U.S.P., is a zinc oxide tinted by a small amount of ferric oxide. *Calamine Lotion*, U.S.P., contains 8 per cent of calamine, 8 per cent of zinc oxide, and 2 per cent of bentonite in calcium hydroxide solution. *Zinc Carbonate, Precipitated,* is a basic zinc carbonate compound of somewhat variable chemical composition, corresponding to not less than 68 per cent of ZnO. Impalpable white powder, without odor or taste. Insol. in water or in alc. *Zinc Stearate,* U.S.P.; a zinc soap, is a white amorphous, insoluble powder.

CADMIUM

In contrast to zinc, which they resemble chemically, cadmium compounds produce acute toxic symptoms even on oral ingestion. They are responsible for some outbreaks of apparent "food poisoning" with violent gastro-enteritis, when acid foods had been in contact with cadmium-galvanized containers, or from cadmium carbonate silver polish (Sovet, 1858). Cadmium fumes are also toxic.

Serious clinical poisoning occurred from cadmium dissolved by acid foods (fruit juices) that had been in brief contact with containers coated with the metal. Very acute gastritis set in almost immediately after ingestion, affecting all who had partaken; but all recovered (S. Frant and Kleeman, 1941). The treatment consists in gastric lavage with sodium bicarbonate, to precipitate the cadmium (W. H. Lufkin and Hodges, 1944). The Sanitary Code of the City of New York prohibits cadmium articles in the preparation or storage of food or drink.

Continued ingestion of small doses (50 to 100 mg. per Kg. of food) by rats causes marked symptoms: bleaching of incisor teeth; severe hyperchromic anemia, stunted growth, and death after some months. The bone marrow is not materially altered. The toxicity is increased by low protein diet. Cadmium diminished the action of phosphatase (R. H. Wilson and De Eds, 1941; A. G. Fitzhugh and Meiller, 1941; J. T. Ginn and Volker, 1944). The chloride is a potent emetic (15 to 25 mg. per cat), and produces nephritis. Hypodermic injections are followed by local necrosis. Intravenously, it kills by arrest of respiration (Alsberg and Schwartze). Intravenous injection of cadmium salts induces ovulation in estrous rabbits, probably through pituitary stimulation (Emmens, 1940).

Inhalation of cadmium oxide fumes produces metal fume fever. The symptoms begin with irritation of the respiratory tract, and may end with fatal pulmonary edema between the fifth and seventh day, in about 14 per cent of the reported cases. Gastro-intestinal irritation may occur if the cadmium is swallowed. There may also be renal irritation. The lighter cases recover in seven to eleven days (P. Ross, 1944; review, L. W. Spolyar *et al.*, 1944).

COBALT

This is one of the indispensable elements. Its administration causes cutaneous vasodilatation and stimulates hematopoiesis to rapid and considerable polycythemia. Its absorption is limited. The local actions are similar to those of copper salts.

Foodstuffs from different parts of the United States contain 0.005 to 0.057 mg. per 100 Gm. of dry substance; leguminous seeds generally more than cereals (Ahmad and McCollum, 1939).

The excretion of cobalt occurs chiefly by the urine, somewhat by the bile and feces (D. M. Greenberg *et al.*, 1943). After intravenous injection of radioactive cobalt salt into dogs, about 5 per cent of the dose is eliminated by the bile in three days, practically none by the pancreatic juice (G. E. Sheline *et al.*, 1946).

Radioactive cobalt, administered to rats on a low mineral diet, shows 80 per cent excreted by the urine, 10 per cent by the feces. The liver retains small amounts for a few days (C. L. Comar *et al.*, 1946).

After oral administration of finely powdered metallic cobalt to man the urinary excretion amounted to 1 to 6 per cent (Penati and Ruata, 1940).

Deficiency Phenomena.—Bertrand and Nakamura, 1934, found that mice died in three weeks when fed on a diet free from cobalt and nickel. Rigg, 1937, reported from New Zealand that "bushsickness" of sheep can be cured and prevented by feeding 8 mg. of cobalt weekly. The liver of the affected sheep was poor in cobalt, averaging 0.002 mg. per 100 Gm., and this rose to the normal, 0.015 to 0.025 mg., when the cobalt was administered. W. M. Neal and Ahmann, 1937, also reported that calves fed on Natal hay free from cobalt develop malnutrition, with microcytic hypochromic anemia, and that this is prevented or cured by feeding 1 mg. of cobalt per day for cattle, 0.1 mg. for sheep. A relatively small excess is harmful. Iron and copper aggravated the cobalt deficiency.

Hematopoiesis.—Waltner and Waltner, 1929, observed marked polycythemia in rats following promptly on the administration of cobalt. Hypodermic injection of 0.1 Gm. of $Co(NO_3)_2$ increased the red count and hemoglobin 20 per cent in twenty-four hours. Addition of 0.5 per cent of cobalt to the food for a month raised the red count to ten or eleven millions, and the hemoglobin to 165 per cent. These gradually returned to normal on discontinuing. The polycythemia occurs in all vertebrates that have been tried, including birds and frogs (J. Sutter, 1934). Dogs require 10 mg. per Kg. daily to produce significant polycythemia (G. Brewer, 1940). The blood volume is increased chiefly by the volume of the cells (J. E. Davis, 1940). It accelerates the recovery of rabbits from the anemia induced by repeated hemorrhage or benzene (W. Kleinberg *et al.*, 1939), but has relatively little effect on x-ray anemia (A. S. Gordon *et al.*, 1942). The cobalt polycythemic animals give better work performance under anoxic conditions (S. S. Dorrance *et al.*, 1943). Orten, 1936, administered clinically 0.1 to 0.5 mg. daily as cobaltous chloride, by mouth or hypodermically. C. R. Baxter, 1939, reports mildly toxic reactions without any benefit, in hypochromic anemia patients.

Cobalt does not increase the anoxic polycythemia in rabbits (J. Goodman, 1947).

The polycythemia is caused by increased hematopoiesis, probably by hyperplasia of the bone marrow;

but its mechanism is not understood (C. O. Warren *et al.*, 1944). It occurs when the marrow is denervated (Q. D. Schubmehl *et al.*, 1943). It is preceded by a significant rise in the proportion of reticulocytes. The bilirubin concentration of the serum is slightly increased. Splenectomy may delay the increase of blood cells (Orten, 1935, 1936) and may prevent it (Berwald *et al.*, 1934). In rabbits, the addition of manganese heightens the action (Kleinberg, 1934). It does not occur if the diet is deficient in copper (J. M. Orten, Underhill *et al.*, 1932). In four dogs rendered anemic by milk diet, the feeding of 0.1 mg. of cobalt daily enhanced materially the utilization of added iron and copper (D. V. Frost *et al.*, 1941; review, M. O. Schultz, 1940).

Cutaneous Vasodilatation.—LeGoff, 1930, 1934, reported that hypodermic injection of 10 to 50 mg. of cobalt chloride, citrate or salicylate, in man dilates the vessels of the face and ear, beginning in three minutes and persisting for fifty minutes. The blood pressure falls about 10 mm. No toxic symptoms were observed. The effect occurs also on oral administration; it is not produced by similar doses of nickel.

Blood Sugar.—Bertrand and Macheboeuf reported that cobalt enhances the hypoglycemic action of insulin. Others have failed to confirm this on dogs (Magenta, 1927) and on standardized rabbits (Blatherwick and Sahyun, 1927).

Toxic Actions.—Intravenous injection of 0.5 mg. of cobalt salts into rabbits produces considerable fall of blood pressure (LeGoff, 1930). Canjolle *et al.*, 1944, report prolonged vasodilatation, chiefly by the diminished excitability and tone of the vasomotor center supported by direct action on arterial muscle. Respiration is increased by direct action and reflex stimulation of the center. Peristalsis is increased after transient inhibition. A. Stuart, 1884, reported that intravenous or hypodermic injection of cobalt or nickel salts affects the central nervous system directly, in addition to the usual metal action on capillaries, heart and kidneys. There are tremors, chorea and convulsions, followed by paresis. In frogs the medulla is stimulated before the spinal cord (A. Stuart, 1884). Some tolerance is acquired.

The urine is increased, and always contains sugar, often proteins. Cobalt salts act as antidotes to HCN poisoning, through the formation of cobalt cyanides. To be effective they must be introduced subcutaneously in doses which are not devoid of danger. They are therefore not used in man.

The toxicity of cobalt (and nickel) for rats is diminished by the sulfur aminoacids, especially by cysteine, but not by choline. This suggests that the cobalt produces its toxic effects by fixing the sulfhydryl group, analogous to arsenic (W. H. Griffith *et al.*, 1942).

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NICKEL

The pharmacologic significance of this metal appears slight. The metal is extensively used, but is not easily soluble, and the salts are not easily absorbed. They are astringent and irritant on local application. Nickel salts have been used as emetics, but are not to be recommended. Nickel cooking vessels give up a harmless trace of the metal to the food (Dzerzgowski and Schumoff-Sieber, 1906, 1908; Lehmann, 1909). Nickel platers are subject to eczema.

Du Bois, 1932, reported 80 per cent of the workers in nickel plants affected. Gaul and Stand, 1934, found 0.01 to 0.09 mg. of nickel per 25 mg. of fresh tissue in psoriasis lesions, in persons not especially exposed to nickel, and never more than 0.01 mg. in normal skin.

Intravenous injection of nickel salts produces fall of blood pressure and the usual flocculation phenomena. The nickel is *excreted* slowly, chiefly by the urine. The urine contains about two-thirds of the nickel of food (N. L. Kent and McCance, 1941). *Hypodermic* injection into mice and frogs is followed by paralyses (Yamagami, 1928). A. Stuart, 1884, described the same effects that he observed with cobalt salts.

With *excised intestine*, dilute solutions of nickel salts produce primary depression, which may be followed by stimulation. Higher concentrations abolish the movements. Nickel is much less toxic than zinc (Salant and Mitchell, 1916).

Nickel Carbonyl.—This gas—$Ni(CO)_4$—is formed by passing CO over finely divided nickel, as in the Mond process of obtaining pure nickel. The phenomena following its inhalation are serious. There is transient malaise, with quick recovery in fresh air; but after twelve to thirty-six hours the patient becomes dyspneic, cyanotic, febrile and delirious, with a blood-stained cough. Death occurs in four to eleven days, with hemorrhages (due to fatty degeneration of the vessel walls) in the lungs, brain and suprarenal glands, and pulmonary edema (Mond, Langer and Quincke, 1890; Armit, 1907, 1908; Brandes, 1934). It is not absorbed as such, but is decomposed by moisture and deposits absorbable colloidal metallic nickel on the respiratory epithelium.

Metal carbonyls in general are volatile liquids that may be absorbed from the skin. *Iron carbonyl* damages the liver severely.

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TIN

Absorption and Fate.—When soluble salts of tin are fed, a small quantity is absorbed and accumulates in the tissues. Of the normal tin income, 50 to 80 per cent is excreted by the urine. After intravenous injection the excretion is also largely by the urine (N. L. Kent and McCance, 1941). When soluble salts are injected hypodermically, elimination occurs slowly, mainly by the alimentary tract, but somewhat by the urine, producing marked injury of the kidneys. Considerable quantities are retained: 20 to 25 per cent in the skin, 5 per cent in the liver (Salant and co-workers, 1940).

The *acute toxicity* of the nonprecipitant stannic or stannous sodium citrate by intravenous injection into rabbits is of the order of sodium citrate, so that the tin salts as such are not acutely toxic. Animals with 25 per cent of the fatal dose recover completely. The tin leaves the blood rapidly. The organ distribution is similar to that of bismuth; the kidneys retain it longest (J. Seifter and Rambousek, 1943). Older observers reported *chronic effects* ranging from gastro-enteritis to ataxia and motor paralyses resembling chronic lead poisoning (White, 1880). Salzer, 1918, reports chronic poisoning resulting from a dental plate of "*Watt's metal.*" There were nervous symptoms and anemia. "*Stannoxyl,*" a proprietary compound advertised for oral and intramuscular administration in boils and styes, was found worthless by J. A. Kolmer *et al.*, 1931.

Tetramethyl tin, when inhaled, causes immediate aliphatic narcosis, followed by temporary paralysis and delayed encephalopathy. Tetra-ethyl tin has similar actions, but is less potent (J. Seifter, 1939).

Tin hydride, SnH_4, is highly toxic to mice and guinea pigs, producing pulmonary irritation and convulsions (F. Paneth and Joachimoglu, 1924).

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MERCURY

Mercury, particularly in the mercuric salts, has a strongly toxic action on protoplasm. Mercurial compounds are therefore potent antiseptic agents, but their usefulness is limited by precipitation, irritation and toxic systemic effects. The local actions depend on the mercury ions, and are absent in organic compounds that hold the mercury in molecular form. Intravenous injection of the mercury-fluorescein dyes (mercurochrome, and so forth) produces colloidal "reactions." The water-insoluble mercury compounds are fairly rapidly converted into soluble compounds, and these are absorbed, distributed through all the tissues and excreted by all channels, but mainly by the urine and feces. Traces remain in the body for many months. Acute poisoning presents chiefly the phenomena of local corrosion, followed later by the characteristic features of systemic poisoning, stomatitis, dysentery and nephritis. In chronic poisoning, nervous symptoms and cachexia appear. Calomel is comparatively insoluble, so that it may be employed as a cathartic and diuretic. The relatively nontoxic organic compounds, such as mercurophylline (mercupurin) and mersabyl (salyrgan), are injected intramuscularly or intravenously as active diuretics; this effect is also produced by small doses of inorganic mercurials. Mercury was the earliest and for centuries the only effective agent for the treatment of syphilis.

Local Actions and Uses of Mercurials.—The application of soluble mercury compounds produces antiseptic, stimulant, irritant and escharotic effects. These depend on the concentration of mercuric ions in the solution, and on the precipitation of proteins. The latter is not a simple function of the ionization, for the protein precipitates redissolve in excess of protein and in a variety of other substances, such as the halide salts of alkalis, especially the iodides; and in alkalis, amides, and so on. When these are present in or added to the mercuric salts, the precipitation of protein is diminished or prevented. Solutions that ionize weakly also fail to precipitate proteins, presumably because they always leave a sufficient excess of protein to prevent precipitation. Absence of protein precipitation diminishes local irritation and favors the penetration of the mercury. In the presence of proteins and in complex culture fluids, the ***antiseptic action*** of such nonprecipitant compounds may therefore appear equal to or greater than that of more highly ionized but more precipitant compounds. From the standpoint of local and antiseptic actions, the mercury compounds fall into three broad groups: (1) the soluble inorganic mercuric salts; (2) the water-insoluble mercury compounds, mostly mercurous, which are dissolved slowly on contact with the tissues; and (3) organic mercury compounds, mercury of which is attached to a benzene ring, and held more or less firmly, so that it ionizes but little.

Ionization of Mercury Compounds.—The following classification is similar to that of F. Mueller, Schoeller and Schraut, 1911, but also takes into account the antiseptic action on yeast cultures, as determined by J. Peterson, 1926. These also give a convenient index of ionization, the restraining effect for equivalent mercury content being expressed in terms of $HgCl_2$ as unit; for instance, "yeast restraint 0.1" signifies that the anti-yeast activity is one-tenth that of mercuric chloride, after making allowance for the difference in mercury content. The individual compounds are arranged according to this coefficient, in descending order. Those in square brackets were not investigated by Peterson, so that their position is conjectural.

Simple Highly Ionizable Inorganic Mercuric Salts.—Yeast restraint, 1.7 to 1; precipitate proteins, but redissolve in excess; greatest local irritation; rust metals; readily precipitated by H_2S = Mercuric chloride ($HgCl_2$). It should be added that the actual ionization of mercuric chloride is not high, but that it can apparently replace the ions readily, so that it behaves chemically as if it were highly ionized.

Moderately Ionizable Mercuric Compounds.—Yeast restraint, 0.6 to 0.35; protein precipitation, slight or absent; irritation relatively slight; rusting of metals slight; precipitated by H_2S = Potassium-mercuric iodide (K_2HgI_4) [or bromide]; mercuric succinimide; sublamine (mercuric sulfate-ethylenediamine); metaphen (aceto-oxymercuri-nitrocresol), requires alkali for solution [Mercurophen (sodium oxymercury-nitrophenolate), Schamberg *et al.*, 1917, 1919].

Poorly Ionizable Mercuric Compounds.—Yeast restraint, 0.06 to 0.01; protein precipitation absent; irritation slight; rusting of metals absent; H_2S precipitates slowly or imperfectly with the lower members = [Novasurol (sodium mercuri-chlorphenyl oxyacetatediethylbarbituric acid)]; mercuric oxycyanide ($Hg(CN)_2HgO$); mercuric cyanide ($Hg(CN)_2$); mercuric benzoate, mercuric salicylate (low yeast restraint because of slight solubility; dissolves on adding alkali); meroxyl (sodium hydroxymercuri-benzophenone sulfonate); mercurosal (sodium hydroxymercuri-salicyl oxyacetate).

Mercuric Fluoresceins.—As class III, but with fluoresceins which play a considerable part in the antiseptic and colloidal shock reactions, for which they are principally used = Flumerin (sodium hydroxymercuri-fluorescein); mercurochrome (dibromo-flumerin).

Insoluble Mercurials.—These become active only by their conversion into soluble mercuric compounds = Mercury iodides and oxides, ammoniated mercury, calomel and metallic mercury.

The **local irritant action** is most pronounced with mercuric chloride, and is especially important in acute poisoning. The coagulation gives an ashy color and cooked appearance to the *mucous membranes* that come in contact with the mercuric chloride. The tissues underneath are inflamed. Prolonged contact leads to necrosis and corrosion. *Intramuscular injections* cause severe pain and sometimes local necrosis. *On the skin*, concentrations of 1 to 5 per cent produce irritation, vesication and corrosion; sensitive skin may be inflamed by the more dilute solutions used in surgical operations. The absorption from the intact skin may be sufficient to produce systemic poisoning. Solutions of 1:1000 to 1:200 are used in the skin diseases (pityriasis, sycosis) for antisepsis and to produce exfoliation of the epidermis.

The local irritation is considerably mitigated by the formation of double salts, as in the potassium mercuric iodide. This may be injected intramuscularly, but not without pain. Its systemic toxicity is about the same as for mercuric chloride, on the basis of mercury content. The organic mercury compounds ordinarily cause little or no irritation in the concentrations in which they are used.

The *water-insoluble mercurials* do not produce immediate effects, but since they are gradually dissolved by the proteins and salts of the tissues, they develop some local irritation and antiseptic action. The latter may be considerable, because of the prolonged and continuous supply of mercuric ions, even though these are of low concentration (Schamberg and Kolmer, 1914). The irritation varies with the rapidity of solution, from practically nothing with calomel, to "stimulation" with mercuric oxide and ammoniated mercury. *Yellow mercuric oxide* is used especially in ophthalmology, as 1/10 to 1 per cent ointment, introduced by Pagenstecher, 1866, for phlyctenular corneitis. Hosford and McKenney, 1933, believe that it is more often harmful than useful. *Ammoniated mercury*, the complex "white precipitate" obtained by precipitating mercuric chloride with ammonia, is employed as 2 to 10 per cent ointment in eczema and parasitic skin diseases, especially pediculosis. It is used against impetigo contagiosa, the official 10 per cent ointment being diluted with zinc oxide ointment to 2 per cent for prophylaxis, 3 to 5 per cent for treatment. This concentration may irritate the skin of the face and neck. Absorption is insignificant, about as with calomel (O. S. Gibbs *et al.*, 1941). *Calomel* is used as dusting powder or ointment for sluggish ulcers, ulceration of the cornea, vesicular conjunctivitis, and so forth. It is nonirritant and may be applied in any concentration. A dusting powder of calomel 3, talc 2, zinc oxide 1 is used to prevent spread of contagious impetigo of the newborn (Swendson and Lee, 1931). A 33 per cent ointment is employed in venereal prophylaxis, and against pediculi. The *mild mercurial ointment*, which contains 30 per cent of finely divided metallic mercury, is used for the destruction of lice, but is liable to cause dermatitis when used on hairy surfaces, even with a single application, so that the calomel ointment is preferred. The *stronger mercurial ointment* (50 per cent) is used in syphilis. The *insoluble mercury compound should not be applied to the eye when the patient is using iodides;* the irritant mercuric iodide is formed on the conjunctiva and causes severe injury. Iodine compounds that do not ionize readily naturally produce but little reaction (Grumme-Fohrde, 1914). Bromides behave like iodides, but chlorides are harmless (Schloms, 1913).

Bacteriostatic Action.—Robert Koch, 1861, popularized mercuric chloride as a potent antiseptic. Geppert, 1889, confirmed that it has a high bacteriostatic potency, preventing the multiplication of many bacteria in dilutions of 1:300,000; but that it is not a reliable germicide, for the bacteria are not killed, but resume growth when the mercuric chloride is removed or further diluted. It is especially ineffective for sporulating organisms, such as anthrax, tetanus and gangrene; anthrax spores exposed to 3 per cent mercuric chloride for seven days are viable after washing with hydrogen sulfide (A. Müller, 1920). This is practically important, as spore-forming bacteria are present in 10 per cent of the knife blades after use in operations (Brewer, 1939). The bacteriostatic potency is therefore misleading and a source of danger. This holds true also for the organic mercurials. These are likewise highly bacteriostatic, but the results of J. H. Brewer, 1939, show that none can be relied upon to sterilize instruments when spore-forming organisms are present, even with the twenty-four hours' contact with the solutions advised by the makers; nor do they kill staphylococcus aureus in thirty minutes. Mercuric chloride is further objectionable by irritating and injuring the tissues; by its systemic toxicity; and by producing rapid corrosion of metallic instruments and gradual deterioration of rubber. The irritant and corrosive effects are somewhat decreased by the presence of an equal or double quantity of ammonium or sodium chloride, as in the commercial bichloride tablets. These form double salts which are less dissociated and therefore somewhat less active (Sabbatani, 1906). Hydrochloric, tartaric and citric acids have similar effects. The result is accomplished more effectively by using the *potassium mercuric iodide;* or the mercuric oxycyanide, cyanide or benzoate, which dissociate less; or the organic compounds.

Definition of Terms.—Much harm has probably resulted from loose conceptions of antibacterial properties. Properly speaking, *germicidal* means actually to kill bacteria; *bacteriostatic,* arrest of their growth and multiplication; *sterilization,* the absence or destruction of all micro-organisms; *antisepsis,* prevention of sepsis and putrefaction; *disinfection* renders an object noninfectious.

Antiseptic Dilutions of Mercuric Salts.—Mercuric chloride and the other inorganic mercuric salts are used outside the body as 1:1000 solution; on mucous membranes, 1:20,000 to 1:2000, with caution as to absorption. A 1 per cent alcoholic solution of mercuric chloride is used on corneal ulcers. *Spermatozoa* (of rats) are immobilized by 0.0003 per cent. [The equivalent spermicidal concentrations of other antiseptics are: permanganate, 0.004 per cent; phenol, 0.07 per cent; quinine, 0.6 per cent; alum, 0.8 per cent (Ishikawa, 1923; quoted by S. Loewe, 1926, in Handbuch der Praktischen Therapie, *1:* 796).] *Pediculi* are killed effectively by applying a 1:500 solution of mercuric chloride in diluted alcohol twice daily for several days in succession to the head, or a 1:2000 solution to the body; but there is some risk of dermatitis (Fantus, 1937). A 1:100 solution in alcohol is used against *bed bugs.* The vapor of metallic mercury at room temperature is highly toxic to insects (H. C. Gough, 1938).

The bacteriostatic action of mercury salts has been attributed to binding of protein *thiol groups* (P. Fildes, 1940). *Saccharase* is poisoned by mercury and silver salts in dilutions of about $1:10^9$, or approximately an atom of the metal per molecule of enzyme (Euler and Mÿrback, 1919). A similar relation holds for silver and urease (Sumner and Mÿrback, 1930).

Potassium mercuric iodide is formed by dissolving mercuric iodide or chloride in an excess of potassium iodide. Mercuric iodide is insoluble in water, but dissolves in the presence of potassium iodide in the molecular ratio of one HgI_2:two KI, forming a complex salt, K_2HgI_4. A slight excess of KI (20 per cent by weight of the potassium mercuric iodide) is required for permanent solutions. This is assured by using equal weights of HgI_2 and of KI (or NaI); but they are often used in the ratio of 3 Gm. of KI (or NaI) for each gram of mercuric chloride.

Mercuric oxycyanide, cyanide and benzoate produce little irritation and have been used as antiseptics on sensitive mucous membranes, such as the conjunctiva and urethra, as 1:4000 to 1:1000 solutions. They have been largely displaced by organic compounds.

Organic mercurial antiseptics were proposed with the hope of securing a better therapeutic index, a wider margin between antibacterial potency and injury. A considerable number of compounds has been introduced in which the local and systemic toxicity of mercury has been greatly reduced by binding it more or less firmly to a benzene ring, without materially decreasing the bacteriostatic power. As bacteriostatics, these compounds are useful for application to mucous membranes, but satisfactory germicidal potency has not been achieved.

The following are the principal commercial compounds of this type in alphabetic sequence, their approximate mercury content, and the dilutions in which they are generally employed: *basic phenylmercuric nitrate* (*merphenyl nitrate*), 63 per cent, 1:15,000; *merbromin* (*mercurochrome*), 25 per cent Hg, 1:100; *meroxyl,* 27.5 per cent, 1:200; *merthiolate,* 49.5 per cent, 1:1000; *nitromersol* (*metaphen*), 56 per cent, 1:2500.

Phenylmercuric ("*merphenyl*") *Compounds,* N.N.R., readily liberate the phenylmercuric radical $(C_6H_5Hg)^+$, which does not precipitate serum proteins or rust metals, but which combines with protein thiol groups to form poorly dissociated protein mercaptides (L. Hellerman *et al.*, 1943). It depresses cytochrome and various other enzyme systems (E. S. Cook *et al.*, 1946). The *basic nitrate* was introduced by L. A. Weed and Ecker, 1931, as a highly potent bacteriostatic agent, with low toxicity for man, ordinarily producing little local irritation. Brewer, 1939, ranks its bacteriostatic potency with the other compounds listed above. Like other mercurials, it is not effective against spores. It is employed as buffered solutions which are more stable and less irritating. It is applied to the skin and superficial wounds as 1:25,000 to 1:15,000 solution. It is marketed as 1:1500 solution which may be applied briefly, but should not be used for wetting dressings. It may liberate mercuric ions under some conditions and become caustic. The *borate, chloride* and *picrate* are also used. *Phenylmercuric acetate* appears to outrank all other contraceptives, experimentally and clinically (N. J. Eastman and Scott, 1944). Very little is absorbed.

Mercurochrome, merbromin, N.F., a bromomercurifluorescein derivative related to eosin, was introduced by H. H. Young *et al.*, 1919. *Eosin* itself is somewhat antiseptic (Noguchi, 1908) and shares many of the properties of mercurochrome.

Mercurochrome is used as a nonirritant *antiseptic.* Solutions of 2 per cent cause only slight and brief smarting of sensitive mucous membranes, such as the urethra. Prolonged contact with 5 per cent solutions, however, is injurious to cells. It is considerably more toxic for bacteria, especially in acid solution (urine of *p*H 6.), but its activity varies greatly for different organisms, even of the same group, and is materially reduced at the neutral point, more so at alkalinity, and by proteins and bile (Birkhaug, 1930, 1933). Altogether it does not rank high as an antiseptic, even in the test tube (Simmons, 1928). Mercurochrome practically does not penetrate normal living tissue, but only such as is dead and dying; it is fixed in the stratum corneum of the skin and of the mucous membranes; and penetrates mucus and wound detritus. A 2 per cent solution is advertised as a first-aid antiseptic, but is ineffective against spore-bearing organisms and against rabies. It forms a thin eschar on burns, but several instances of severe mercury poisoning have been reported (A. M. A. Councils, 1944). A 2 per cent solution in an acetone-alcohol-water mixture has been advocated for preoperative skin disinfection, but it is unreliable (von Oettingen *et al.*, 1931). Mercurochrome is *marketed* as iridescent green scales or granules, permanent in the air, freely soluble in water, soluble in alcohol, insoluble in chloroform or ether. Its aqueous solution is of a deep cherry color, and is stable. It is incompatible with acids, with most alkaloidal salts and with local anesthetics.

Intravenous injection of mercurochrome was introduced by Young *et al.*, 1926, to combat septicemias and certain localized infections, but has practically gone out of use. It produces a shock reaction which is sometimes followed by prompt improvement; but it is ineffective in many cases and not without danger. Positive results are presumably due to the flocculation shock, for the body fluids (blood, bile, knee joint) are not even bacteriostatic (Hench, Snell, Greene *et al.*, 1925). The drug is injected, in the dosage of 5 mg. per Kg. of body weight, as a freshly prepared and filtered 0.4 per cent solution in distilled water. It is self-sterilizing and should not be boiled

It generally causes a febrile reaction, with chill, nausea and sometimes also profuse diarrhea; but a single injection of this dosage is reasonably safe. Severe symptoms and occasionally serious collapse sometimes occur between 5 and 7.5 mg. per Kg. Stomatitis is also sometimes seen. *Rabbits* show severe but usually temporary renal damage with 5 mg. per Kg.; 25 mg. may be fatal. Their susceptibility is evidently greater than with men or dogs, but the margin of safety is not wide.

Excretion.—The mercurochrome leaves the blood stream rapidly. It is excreted mainly by the bile and stools, some by the urine (Hench *et al.*, 1925). However, gallbladder carriers of Bacillus typhosus could not be disinfected by mercurochrome, by vein or by mouth (K. F. Meyer *et al.*, 1926).

Sodium-p-hydroxymercuribenzoate was recommended by M. T. Hanke, 1940, as an oral antiseptic. It is relatively nontoxic (T. J. Haley and Edwards, 1947).

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ABSORPTION AND FATE OF MERCURY

Mercury compounds and metallic mercury are absorbed readily from all surfaces, even from the intact skin, and all these channels are utilized therapeutically. Chemical changes occur in the course of the absorption. Mercurous compounds and metallic mercury are oxidized; the mercuric salts from soluble compounds with the proteins, sodium chloride and alkalis (Voit, 1857). The absorbed or injected mercury leaves the blood rapidly, except for small traces. A part is excreted by the urine and feces (Welander, 1886), the fecal excretion being generally the less important. Variable traces are generally found in the bile, sweat (Tachau, 1911; Lambert and Patterson, 1915), gastric (Lieb and Goodwin, 1915) and intestinal juice and saliva (literature in Lomholt, 1928). The excretion declines rapidly and becomes insignificant within a week after the administration ceases (unless absorption depots are maintained), but traces may be excreted intermittently for six months or longer. A considerable proportion of the absorbed mercury is *retained* indefinitely in the body: 50 or 60 mg. with therapeutic courses of intramuscular or intravenous injections of soluble inorganic or organic compounds, and 200 to 700 mg. with intravenous injections of colloidal solutions (Cole, Sollmann and Schreiber). The excretion will be further discussed in connection with the clinical use. The *mercury concentration in the blood* falls rapidly, even after intravenous injection, to traces about equivalent to those in the urine. Similar concentrations exist in the other body fluids. The distribution in the organs is similar after the therapeutic use and in acute poisoning.

Normal Mercury Content.—Nearly all foods contain tangible traces of mercury, giving a normal income of about 20 micrograms daily. The daily urinary excretion averages 7.6; fecal, 4.8; total, 12.4 micrograms. Kidneys of men without history of mercury exposure contain about 50 micrograms, animals about 25 per 100 Gm. (O. S. Gibbs *et al.*, 1941).

After clinical *acute and fatal bichloride poisoning*, the quantity in the organ is surprisingly uniform, although dosage does have some effect. The concentration is always highest in the kidneys (average, 3.8 mg. per 100 Gm. of fresh organ); then comes the liver, with about one-half to two-thirds of the kidney concentration; the spleen with one-seventh, the intestines with one-ninth; the heart and skeletal muscle and lungs with one twenty-fifth (= 0.2 to 0.3 mg. per 100 Gm.) and finally the blood, with 0.015 to 0.12 mg. per 100 cc., about one-fortieth of the kidney concentration. Edema fluids are still lower. The bile is variable, but always higher than the blood. The total content of the liver is about three times that of both kidneys. From these data, the mercury generally retained in the entire body can be estimated as about 240 mg., which would be close to the intravenous fatal dose (Sollmann and Schreiber, 1930. The older analyses are reviewed by Lomholt, 1918). The amount stored in the kidneys and liver furnishes an index of the amount absorbed, for instance, from percutaneous application to rats (E. P. Lang, Vox *et al.*, 1946). In therapeutic administration, the mercury *level of the blood* is said to run between 0.4 and 2 mg. per liter, which approximates the concentration in the urine: 2 to 3 mg. per liter is rare, and is generally accompanied by toxic manifestation. Young and Taylor, 1929, claimed that mercury is bound in the bones similarly to lead. It passes through the placental circulation, and it is claimed that congenital syphilis may be treated by mercurial inunction of the mother (Jung, 1914). The concentration in the amniotic fluid was found of the same order, 0.2 to 0.6 mg. per liter. The data for cerebrospinal fluid (Young and Taylor, 1929) are contradictory and probably not reliable. In animals, the *colloidal forms* of mercury, including the dyes, are found chiefly in the liver, after intravenous injection. With mersalyl, intravenously, the highest percentage was in the bile, suprarenals, kidneys and large intestine (J. Müller, 1929). After sojourn of guinea pigs in an *atmosphere saturated with mercury vapor* (6 mg. per liter at 13° C.) for ten hours to four days, the highest concentration was also found in the kidneys, relatively little in the liver (Holtzmann, 1931).

Form of Mercury in the Tissues.—The slowness of the excretion indicates that this is firmly bound, and presumably insoluble. The black line, sometimes seen on the margin of the gums, consists apparently of mercuric sulfide (Almquist, 1912), but this is not typical of its general distribution. It indicates, however, that the circulating mercury is ionized at least in part, presumably as a mercuric albuminate: sodium chloride compound. Eckmann, 1896, described the histochemical tests. The *globules of metallic mercury* reported in necrotic bone and in the tissue of an aortic aneurysm (Kolmer and Martin, 1918) are a curiosity. Colloidal mercury compounds when injected intravenously are presumably retained by the reticular endothelium. The *forms in which mercury is excreted* are also not fully known, but the greater part of the urinary mercury can be deposited by electrolysis and is therefore ionizable (Lomholt, 1928). Young and Taylor, 1929, claimed that the mercury excretion is temporarily suspended by calcium lactate (6 Gm. by mouth), and increased by low calcium income and ammonium chloride administration and by sodium thiosulfate. Confirmation by other analytical methods appears desirable. Blumenthal and Oppenheim, 1911, claimed that potassium iodide diminishes the deposition in the liver.

Toxicology.—*Acute* mercurial poisoning occurs generally from mercuric chloride; ***sub-acute***, from therapeutic overdoses; ***chronic*** mercury poisoning may occur medicinally, but is seen especially in industrial poisoning (workers in mercury, manufacturers of thermometers, mirrors, electric lamp bulbs, felt, and so forth). A large proportion of those exposed to mercury are affected, because the adherence of the metal to the skin, and the inhalation of its vapor make protection difficult.

Phenomena of Acute Poisoning with Mercuric Salts.—The immediate effects are due to coagulation, irritation and superficial corrosion, to which mucous membranes are highly susceptible. There is an astringent metallic taste, salivation; burning, swelling and ashy discoloration of the mouth and pharynx; thirst, abdominal distress and pain, at first epigastric, then diffused; vomiting with white or often bloody mucous shreds; sometimes edema of the glottis. The primary symptoms generally yield to local treatment, including abstinence from food for thirty-six hours; and the patient may be fairly comfortable. The light cases are practically well on the next day. Signs of mercurial stomatitis usually develop in twenty-four hours, but are not especially marked. *Severe cases* give the general picture of serious illness, even in patients who recover: great weakness and prostration or excitement; weak, rapid heart; fall of blood pressure; cramps in the legs; dehydration; stupor; collapse. Death may exceptionally ensue in a few hours by circulatory collapse (Mering, 1880).

The *viscosity of the blood* (not of the serum) is doubled in mercurial, lead and phosphorus poisoning (Farmachidis, 1912). A neutrophile *hypoleukocytosis* is a constant phenomenon (Donzello, 1915), but in the cases which go on to colitis and nephritis this is followed in a few hours by a marked increase. Counts above 30,000 are unfavorable (L. A. Kohn, 1936).

Somewhat later, the large intestine and kidneys become involved. Within two or three days, the *urine* becomes scanty and shows protein and casts. Anuria may be complete, with death within a week by nephritic pulmonary edema or nitrogen retention, without uremic convulsions. In the event of recovery, the urine may resume about the fifth day. Early anuria augurs a bad prognosis. Cases that begin with polyuria generally recover. If the nephritis is not extreme, membranous *colitis* is likely to develop, with dysentery, tenesmus, ulceration and hemorrhage. These phenomena may only appear, and prove fatal, several weeks after taking the poison (Lambert and Patterson, 1915). There may be toxic anemia with complete lack of blood regeneration (R. Wankmüller, 1944). All but the local symptoms are similar, by whatever channel the mercury was administered. *Postmortem examination* shows the mucous membranes of the upper digestive tract of an ashy color, congested and corroded. The colon lesions are those of severe dysentery: hemorrhage, congestion, coagulation and black ulcerations. The kidneys show acute nephritis, often with calcification of the epithelium.

The gross and microscopic pathology was well described by Eckmann, 1896. It is similar in man and experimental animals, except that with herbivorous animals the chief site of the *intestinal lesions* is in the cecum and appendix, while in man the colon is most affected.

Mercurial Nephritis.—The kidneys are especially susceptible to irritation and injury by mercury. Acute poisoning is followed by severe acute nephritis, primarily tubular, but involving also the capillary endothelium, especially in the glomeruli. Severe poisoning may show hemorrhagic glomerular nephritis. In nonfatal cases, the nephritis tends to become interstitial and eventually cirrhotic. In milder and slower intoxication, the type is primarily interstitial. The susceptibility to nephritis varies considerably even experimentally (W. C. Hunter, 1929). Temporary albuminuria is not uncommon in the therapeutic course, and enjoins caution, although the damage is rarely permanent. In severe acute poisoning, the lumen of the tubules, and sometimes the epithelium, may contain crystals of calcium oxalate (Saikowski, 1866), which have not been explained. They may appear forty-eight hours after the administration (Schamberg *et al.*, 1915). The functional changes in severe acute poisoning consist in intense albuminuria, partial or complete suppression of urine, diminished phenolsulfonphthalein output, retention of urea, rapid reduction of alkali reserve (MacNider, 1917). Smaller doses produce polyuria (Schlayer and Hedinger, 1907), which is utilized therapeutically for diuresis. Renal glycosuria may result from intermediate doses (Franck, 1913).

The anatomical and chemical changes in acute clinical mercury nephritis are described by W. R. Campbell, 1917; those in the subacute form by Foster, 1915. The lesions involve the distal half of the proximal convoluted tubules in frogs; practically the entire tubules in cats; the entire tubules and the duct system in rabbits; and the ascending limb of Henle's loop in guinea pigs (J. G. Edwards, 1934). The usual lethal doses produce acute epithelial necrosis, almost exclusively in the central part of the proximal convoluted tubules (J. G. Edwards, 1942). There is no parallelism between the degree of renal injury and the mercury content of the kidneys (R. Müller and Scheiner, 1936). The *urine changes in acute oliguria* are those of nephrosis: high albumin content; high urea, to 2 per cent; high specific gravity, to 1.030; low chloride, down to 0.01 per cent. The blood plasma shows decreased chloride, and increased nonprotein nitrogen, ten or twenty times the normal. Such patients may recover or may die of nitrogen retention even though the urine flow returns. In favorable cases restoration is accompanied by greatly increased excretion of the retained chloride and urea. Renal epithelium that has regenerated after mercurial injury is more resistant (W. De B. Mac Nider, 1941). In *more prolonged poisoning*, the urea and specific gravity are low, as well as the chloride, although the blood nonprotein nitrogen is high (to 340 mg. of urea N). Uric acid and creatinine are also high in the blood. The alkali reserve is lowered (Leschke). *Hypoproteinemia*, produced by plasmapheresis, protects dogs against mercury injury, but only if it preceded the mercury administration (R. L. Holman and Donnelly, 1942).

Hepatic degeneration of moderate degree was reported in experimental poisoning by Morel, Mouriguand and Policard, 1912. In acute poisoning there may be *glycosuria* and disappearance of glycogen. MacNider, 1919, found that dogs poisoned by mercuric chloride, 15 mg. per Kg., by mouth, react with severe gastro-enteritis, but usually recover. The liver of these animals shows degenerative changes, beginning with deposition of fat in the cells around the central veins, then cloudy swelling and necrosis, the process extending toward the periphery. The intensity is parallel to the nephritis, rather than to the gastro-enteritis. Kunkel, 1889, reported that the *intestines* of rabbits poisoned with mercury show black markings which follow the course of the blood vessels. They are probably hemosiderin formed from the iron liberated by extravasation of blood in the intestinal mucosa (Eckmann, 1896). The rapid *destruction of blood* in mercury poisoning also leads to deposition of hemosiderin in many organs. If the animal recovers, the injured *hepatic and renal cells* are replaced by epithelium of less differentiated and more resistant embryonic type.

probably with eventual restoration of normal cells (W. De B. MacNider, 1942).

The *toxicity of mercuric chloride* varies according to the promptness of the emesis and the individual resistance to the colitis and nephritis, so that the fatal dose is inconstant even for intravenous injection. The prognosis is bad if 1 Gm. or more of mercuric chloride has been taken by mouth, unless vomiting occurs within a few minutes; 0.5 gm. causes severe poisoning, but is ordinarily survived even without vomiting. Other soluble mercuric salts, the double iodide, cyanide (Gettler, 1916), and so forth, have approximately the same toxicity.

Mercuric chloride taken by mouth in doses of 1 Gm. or more, in a series of thirty-eight cases (S. Goldblatt, 1928), produced little effect if vomiting occurred within three minutes; if this was delayed to five minutes, toxic phenomena set in, but generally ended in recovery; with a delay of ten minutes, the outcome was uncertain; with thirteen minutes, most patients died, and with more than fifteen minutes the result was invariably fatal. The dosage of 0.5 Gm. produced severe effects, but ended in recovery, even without vomiting. In the series of Peters *et al.*, patients who had taken less than 1.5 Gm. generally survived (nine fatal cases in thirty-seven); with more than 2 Gm. the outcome was generally fatal.

The toxicity of the *water-insoluble mercuric salts* varies with their solubility in the digestive tract. This is high with the mercury iodide, low with sulfide (Niklasson and Santesson, 1926); the oxide and ammoniated mercury are intermediate. The *insoluble mercurous compounds* are generally less toxic. *Calomel* ordinarily produces only diarrhea even with large doses, but severe and even fatal effects are recorded (for children with 0.4 Gm.; for adults with 2 to 3 Gm.). Fatalities have been reported from *intramuscular injections* of 0.22 Gm. of mercuric salicylate and 0.1 Gm. of calomel. *Metallic mercury*, when finely divided as in "gray powder" (mercury with chalk), is probably more active than calomel.

Metallic mercury, in bulk, formerly given in ileus in doses of 100 to 500 Gm., usually passes off by the feces with little effect; sometimes there is diarrhea and stomatitis; and exceptionally, severe and even fatal poisoning; "and then, a ride in the hearse" ("et postea vectio in curru"), was Archibald Pitcairn's dry comment on the use of mercury in ileus "ad uncias aliquot, vel etiam libras" (Elementa Medicinae, 1740). An attempted suicide by *intravenous injection of metallic mercury* is quoted by Leschke, 2 cc. (27 Gm.) being injected into the right cubital vein. There were no symptoms for three days; then moderate subacute mercurial symptoms which subsided completely. X-ray examination showed mercury globules through the base of the lungs and in a pool in the apex of the right heart. The patient survived ten years in good health, except for occasional diarrhea.

The *toxicity of the organic mercury compounds* is relatively low, increasing with the ease of ionization (Abelin, 1912; Tsungmig Tu).

E. Fourneau and Melville, 1931, found that the intravenous toxicity is not directly related to the chemical reactions of the compound toward NaOH or H_2S, and so on, but rather to the primary linkage of the mercury. The mercurial dyes run irregularly (Klages and Schreiber, 1914). Eight commercial samples of *mercurochrome* varied to 3.5 times in their toxicity to mice (Burn and Elphick, 1930). The *diuretic compounds* will be discussed under that heading. *Fulminate of mercury*, $Hg(CNO)_2$, which is used in munitions, causes local irritation of the exposed mucosae and of the skin, especially of the face and hands, producing sensitization (L. Schwartz, 1944) The volatile *alkyl mercury compounds*, dimethyl and diethyl mercury, are highly toxic. The symptoms are almost exclusively nervous. Inhalation of *methyl mercury compounds* produced tremor, ataxia, dysarthria, gross constriction of the visual field. Memory and intelligence were not affected. Histological damage of the central and peripheral nervous systems was observed in rats and monkeys exposed to methyl mercury iodide (D. Hunter *et al.*, 1940). Two deaths from exposure to the fumes of *diethylmercury* were reported by W. H. Hill, 1943. Serious nervous and circulatory symptoms, which may last for weeks or even months, follow rather slight and brief exposure to the vapor. It is claimed that symptoms may not occur until several months after the initial absorption, and run a fatal course.

Intravenous injection of small doses of mercuric chloride produces *emesis*, which Hatcher and Weiss, 1923, inclined to refer to reflexes from the heart. Larger doses cause flocculation shock. The heart develops pathologic rhythms (F. D. McCrea and Meek, 1929). Small doses of nonprecipitant mercury salts (succinate, 1 to 2 mg., cat) increase the excitability of the vagus to faradic stimulation, and antagonize atropine. Larger doses depress the vagus response. They also greatly increase the toxicity of potassium. Conversely, the administration of calcium alters the response of the heart to mercury (W. Salant, 1924; W. Salant and Nadler, 1927). *Glycolysis in extracts of frog muscle* is inhibited by low concentrations of mercuric chloride or phenylmercuric chloride. This is prevented by the addition of cysteine or glutathione (Gemmill and Hellermann, 1937).

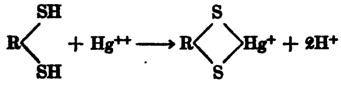
Treatment of Acute Mercuric Poisoning.—The absorption of mercury is prompt, or at least its fixation in the mucous membrane, so that the fate of the patient is practically decided within the first ten or fifteen minutes. If the stomach is evacuated in that time, usually by spontaneous vomiting, the prognosis is hopeful; treatment after this period accomplishes little, although gastric lavage must be tried as a routine. The customary antidotes (egg, milk, calcium sulfide, sodium thiosulfate orally or intravenously, or hypophosphite) are ineffective after this time (S. Goldblatt, 1928). Dimercaptopropanol (BAL) appears especially effective (A. M. Ginzler, 1946; W. T. Longcope and Leutscher. 1946), as it acts after absorption as well as locally. So also does sodium formaldehyde sulfoxylate, introduced by S. M. Rosenthal, 1934, 1946.

Colon lavage, or repetitions of the gastric lavage, and diuresis, do not remove significant quantities of mercury, and would be useful only against the irritation.

Removal of Mercury by Gastric and Colonic Lavage, Feces and Urine.—The impossibility of effective treatment along these lines is illustrated by the quantitative mercury determination of Sollmann and Schreiber, 1936, in four clinical cases of acute mercuric chloride poisoning, two light and two fatal, subjected to extensive and repeated gastric and colonic lavage. The total amount of poison recovered by all these washings, and by the stools and urines, amounted only to 23 to 164 mg. of mercury, 1½ to 3 per cent of the amount taken, and practically all of this was in the first gastric lavage. The colon lavage removed only 1.4 to 9 mg.; and the urine only a total of 1.5 to 9.7 mg. in the first five days. The severe cases had anuria, the mild cases polyuria, but in all the mercury concentration in the urine was within the range of therapeutic administration, indicating that the nephritis is not caused by mercury excreted into the urine, but by that circulating in the blood during the period of active absorption; for the low mercury concentration of the urine also indicates that the mercury disappears promptly from the circulation.

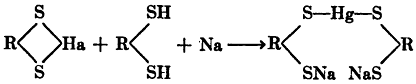
Chemical Precipitants and Adsorbents.—*Proteins* precipitate mercuric chloride, but the precipitate would redissolve, so that they would be useless, except as demulcents, unless they were administered immediately with the poison, to delay its absorption till evacuation. For this purpose, three raw *eggs* may be taken with a quart of *milk* (Sollmann, Barlow and Biskind, 1927). *Charcoal* (a tablespoonful) acts similarly, but by adsorption (Ferreira and MacBride, 1914). It is recommended by Leschke, who claims that 1 Gm. of animal charcoal binds 850 mg. of mercuric chloride. The stomach should be washed with a suspension of three or four tablespoonfuls of the carbon. *Potassium iodide and quinine* (a reversal of Mayer's reagent) was proposed as precipitant by Hall, 1914, but it would accomplish nothing more than the preceding (Barbour, 1915).

Dimercaptopropanol (*BAL*) reacts with Hg^{++} *in vitro* (Gilman, 1946) to form an insoluble mercury mercaptide.



$$\mathrm{R}{<}^{\mathrm{SH}}_{\mathrm{SH}} + \mathrm{Hg}^{++} \longrightarrow \mathrm{R}{<}^{\mathrm{S}}_{\mathrm{S}}{>}\mathrm{Hg}^{+} + 2\mathrm{H}^{+}$$

This reacts further with BAL to form a soluble compound which is probably nontoxic and is rapidly excreted:



$$\mathrm{R}{<}^{\mathrm{S}}_{\mathrm{S}}{>}\mathrm{Ha} + \mathrm{R}{<}^{\mathrm{SH}}_{\mathrm{SH}} + \mathrm{Na} \longrightarrow \mathrm{R}{<}^{\mathrm{S-Hg-S}}_{\mathrm{SNa\ \ NaS}}{>}\mathrm{R}$$

Reducing agents have been tried, on the basis that mercurous compounds are much less toxic than mercuric. They are effective in the test tube, and against whatever unabsorbed mercury remains in the stomach—but no more so than evacuation. Calcium sulfide and sodium thiosulfate were also tried intravenously, but even if they could act in the blood, which is doubtful, they would not be of much use after half an hour, when the mercury has gone into the tissues and the injury has been done.

Phosphite and Hypophosphite Reagents.—Sodium phosphite reduces mercuric chloride to calomel. Its use with sodium bicarbonate as an antidote was proposed by Linhart, 1917, although it is better known as "*Carter's antidote,*" a mixture of sodium phosphite and sodium acetate. Phosphite mixtures are quite successful if given within five minutes after the poison (Fantus and Hyatt, 1917). They are useless after it has been absorbed, even if the antidote is injected into the blood (Sansum, 1918).

Sulfides.—Wilms, 1915 to 1917, made the improbable claim that calcium sulfide is effective even when started twelve to twenty hours after the poisoning. He uses it by mouth (0.15 to 0.3 Gm. every hour) and intravenously (in quantity equal to that of the mercury) as a freshly made, boiled and filtered, 0.2 per cent solution. This is supposed to form mercuric sulfide. The advisability of the intravenous treatment is doubtful. Haskell and Courtney, 1917, found the benefits no greater than with simple saline.

Sodium thiosulfate has been suggested, both orally and intravenously. It acts not only as a reducing agent, but forms soluble double salts with mercurous compounds, which are probably quite toxic. It does not save dogs that have received a fatal dose of mercuric chloride (Melville and Bruger, 1929). J. G. Edwards, 1934, found that it diminished the renal injury, but did not prolong life.

Sodium formaldehyde sulfoxylate was introduced by S. M. Rosenthal, because it arrests the toxic action of mercuric salts promptly on contact, in the stomach and in the blood, but presumably not in the cells. It is ineffective after these have been injured by the mercury (H. Brown and Kolmer, 1934), but it is highly effective under suitable experimental conditions, against intravenous as well as oral administration of mercuric chloride. Injected intravenously shortly after hypodermic injection of mercuric chloride, it protects the kidneys completely against twice, and partially against three times, the fatal dose (Rosenthal, 1935). Modell *et al.*, 1937, find that this would be the limit of the protection against intravenous injection, since the compound that is formed has itself a toxicity of one-third to one-half that of mercuric chloride. Large doses of sulfoxylate increased the toxicity. Alkali injection increased its effectiveness against orally administered mercuric chloride. The *clinical usefulness* of the formaldehyde sulfoxylate is restricted by the delays incident to clinical poisoning. However, the cases in which it has been used generally had a favorable outcome. Rosenthal, 1934, advises the following routine: gastric lavage with 5 per cent of the salt, leaving about 200 cc. in the stomach; followed immediately by 10 Gm.

in 100 to 200 cc. of water (freshly prepared, or ampuls), by slow intravenous injection during twenty to thirty minutes. If necessary, another injection of 5 to 10 Gm. may be made in four to six hours. It is not toxic in the doses advised; animals tolerate 1 Gm. per Kg. intravenously, without symptoms.

The *acute and delayed shock* of mercury poisoning are due largely to dehydration from salt depletion (indicated by decrease of plasma chloride and protein), which is caused by the impaired absorption of fluid from the digestive tract, on account of the nausea, emesis and cell injury (Peters). This would suggest abundant intravenous injection of saline solutions, but administration of fluid beyond the excretory capacity of the kidneys entails risk of pulmonary edema and cardiac failure. It should only be pushed if the blood volume is diminished.

Saline Infusions, Alkalis, and the Like.—Sansum, 1918, determined the minimal fatal dose of mercuric chloride by intravenous injection for dogs as uniformly 4 mg. per Kg. This was not modified by the infusion of plain saline or by sugar solutions, alkalis, Fischer's solution, and so forth; *i. e.*, these were all unsuccessful against acute poisoning. Burmeister, 1917, claimed that *venesection and transfusion* diminish the renal changes. The use of *alkalis* is justified by the observations of MacNider that they protect the kidneys against metallic poisons. However, their success is probably limited.

Subacute phenomena develop in sequence to the acute symptoms; or independently of these if the mercury is introduced more gradually, with too intensive or excessively prolonged therapeutic administration, or in the course of chronic industrial or accidental poisoning. They consist in localized chronic inflammations, especially stomatitis, colitis, nephritis and more rarely dermatitis. The stomach and small intestines usually escape (review, Almkvist, 1928). The phenomena merge into those of the chronic poisoning and may be considered in that connection.

Chronic Mercury Poisoning.—Long-continued exposure to relatively small doses leads to a slow and insidious development of chronic poisoning, usually with some stomatitis and renal irritation, but with additional nervous and nutritional disturbances; especially characteristic tremors, erethismus (psychic irritability and restlessness) and other psychoses; cachexia with anemia, malnutrition and muscular atrophy; bone changes (decalcification) and more rarely neuritis or pareses. Abortion is common. It is doubtful whether *treatment* materially influences the course after the appearance of symptoms. Potassium iodide and hot baths are generally tried, with the intention of hastening elimination, but their effectiveness has not been established. Buchtala found that the iodide rather delayed the urinary elimination of mercury. Prophylaxis is therefore more important. Those who work much with mercury should be protected against unnecessary exposure (review, L. T. Fairhall, 1945).

Industrial chronic poisoning by mercurial solutions is illustrated by the study of Neal and Jones, 1937, on the cutting of fur for hat felting, where the workers are extensively exposed to mercuric nitrate. (It is being displaced by nonmercurial technics; P. A. Neal, Flinn *et al.*, 1941.) Of the 500 operatives examined, about a twelfth showed definite mercurial symptoms, especially nervous. All these had fine intention tremors and three-fourths had psychic irritability. Stomatitis and renal disease were not conspicuous and were indeed doubtful. The urine of two-thirds contained less than 0.01 mg. per liter, the other third, 0.01 to 0.79 mg.; only one above 1.2 mg. The incidence of positive Wassermann tests was 2.5 per cent, as against 3.5 to 4 per cent in other industries; but it is not certain that the difference signifies resistance to syphilitic infection. Acute and chronic poisoning in the *tungsten and molybdenum industry* was reported by L. Lewis, 1945. Leschke claims that the urinary excretion of mercury in exposed workers may exceed 20 to 80 mg. per day, with only moderate symptoms; but ordinarily it is about 0.1 mg. without symptoms.

Toxic Income.—O. S. Gibbs *et al.*, 1941, consider that continued absorption of 5 mg. daily is only occasionally deleterious. They incline to believe that chronic organ toxicity depends on the organ content, 0.1 mg. per 100 Gm. being harmless, while 0.8 to 1 mg. may be harmful. A. Stock, 1943, estimates the *normal daily urinary excretion* of mercury is 0.1 to 1 microgram.

Amalgam Tooth Fillings.—A few cases diagnosed as chronic mercury poisoning have been ascribed to copper amalgam (Fuehner, 1927; Fleischmann, 1928; A. Hertz, 1929); none to silver amalgam. Some doubt is justified as regards the copper amalgam. The symptoms were not particularly distinctive. Borinski, 1931, found the daily urinary mercury output in patients with copper amalgam fillings at most 1.6 mg. on the third day, and 0.02 mg. after a year, the latter about twice the output of persons without special exposure. Silver amalgam gave about half of these levels.

Mercury Vapor Poisoning.—Metallic mercury vaporizes at ordinary temperature, and more rapidly if heated. The heated vapor condenses on the respiratory mucous membranes and in the mouth, whence the mercury may be swallowed or oxidized in situ to absorbable compounds. These give rise to focal irritation, for instance in the lungs (Ricker and Hesse, 1914), and to systemic effects. Mercury volatilized at room temperature is absorbed directly, as such or after oxidation.

Mercury vapor poisoning occurs in various industries and was not uncommon among scientists. Stock, 1929, deduced from the biographies that Faraday and Pascal were so afflicted, without being aware of the cause. There are some indications that traces of mercury vapor diffuse through thin moist membranes as dissolved metal (it does pass in this manner through several centimeters of oil, and vaporizes again from the surface, so as to amalgamate a strip of copper suspended above the oil). It is also conceivable that the metal may circulate and be excreted in this form, since the urine does not give the mercury ion reactions until it has been oxidized. Henderson and Haggard give the following as the mg. of mercury in a liter of air saturated at the temperatures as stated: 20° C., 0.015 mg.; 30°, 0.034; 40°, 0.07; 100°, 3.26. (Multiplication by 1000 gives the mg. per cubic meter.) Such saturation would rarely be attained under working conditions. It should be remembered that the rate of volatilization increases with the surface exposed and with the subdivision of the mercury.

Concentrated mercury vapor may produce grave subacute poisoning, as with the crew of the British sloop Triumph, in 1810. In salvaging a mercury cargo, 200 sailors were severely poisoned, and three died (cited by Brouardel). The more dilute vapors, encountered in mercury mines, factories and laboratories, gradually produce the phenomena of chronic poisoning, tremors, stomatitis (rather uncommon, Merget, 1889) and some digestive derangements.

M. Shepard *et al.*, 1941, found up to 0.07 mg. per cubic meter in the *air of scientific laboratories* without any mercurial symptoms. They consider that there is little danger below 0.1 mg., and this is generally accepted as the *permissible limit.* Toxic symptoms are observed after two or three months or later, in men exposed for three to five hours per day to concentrations of 0.02 mg. of mercury per cubic foot of air (0.0007 mg. per liter), the daily absorption being estimated as 0.8 to 1.3 mg. (Turner, 1924). These dilute mercury vapors may be fatal to small animals, but not usually to man. The daily excretion may be fairly large, 2 to 7 mg. in men with therapeutic inhalations (Bürgi, 1906). *Dogs* exposed for eight hours daily to air with known concentrations of mercury (mg. per cubic meter of air) gave the following results (A. M. Fraser *et al.*, 1934) which are probably fairly applicable to man: 1.9 mg. for forty days did not produce recognizable mercury effects. The lowest concentration which invariably resulted in chronic intoxication was 3.05. When toxic symptoms appeared, the daily urinary mercury excretion was 0.5 mg. in a dog of 12 Kg., equivalent to 3 mg. for a man of 72 Kg. With air concentrations of 3 to 26 mg., about a fourth of the inhaled mercury was absorbed. *Guinea pigs* exposed ten hours daily for four days to 6 mg. per cubic meter showed marked hemorrhagic colitis and neurotic symptoms. The greatest storage was in the kidneys, little in the liver (Holzmann, 1931). *Rabbits* reacted unequally; some responded promptly with salivation, tremor and loss of weight; others showed no symptoms after several months of exposure (Kulkow *et al.*, 1932).

Tests for Mercury Vapor.—This can be visualized by interposing it between a mercury resonance lamp and a screen of anthracene (Leighton and Leighton, 1935). Other methods of detecting small amounts are reviewed by Goodman, 1938.

Stomatitis is usually the earliest symptom of excessive therapeutic use or of chronic poisoning. It occurs about as readily when the mercury is administered otherwise than by mouth. It begins with fetor, then metallic taste, soreness of the gums and some salivation (ptyalism). This is as far as the therapeutic use should go. If it is pushed further, the teeth loosen, the edges of the gums blacken and they, and later the tongue, become swollen and ulcerated. The irritation and infection cause severe salivation and progressive exhaustion and sometimes fatal ulcerative stomatitis. With a more chronic course of severe poisoning there may be loss of the teeth and necrosis of the jaw. The *susceptibility to stomatitis* varies greatly and is markedly influenced by the hygienic condition of the mouth and teeth and by other individual factors, as well as by the dosage of mercury.

The stomatitis is most effectively *prevented and treated* by hygiene and care of the teeth. Septic conditions about the gums are especially detrimental, and should be corrected before mercury is started. Hydrogen peroxide or potassium chlorate (a tablespoonful of the saturated solution to a glass of water) should be used as a mouth wash several times a day. The use of tobacco is said to be injurious.

The *mechanism of the stomatitis and colitis* is probably connected with the local precipitation of mercuric sulfide which occurs in the capillary endothelium in these situations, being formed by the interaction of putrefying material with the circulating ionic mercury. This sulfide is toxic to the cells with which it is in contact, and the injured and necrotic tissue furnishes a starting point for ulcerative micro-organisms, especially the B. fusiformis and the Treponema dentium in the mouth and the colon bacillus in the large intestines, the latter giving rise to different lesions. Analogous conditions arise also in necrotic tonsils. The ulceration is, therefore, an indirect effect, resulting from invasion of special micro-organisms through a nidus prepared by the precipitation of mercuric sulfide. This explanation, which originated with Almkvist (1906, 1912, 1916), accounts for the variations of susceptibility and for the exclusive location of the ulcerations in situations where putrefactive processes produce hydrogen sulfide. The stomatitis always starts as gingivitis, in "gingival pockets" which invite putrefaction. It does not develop in infants and old people without teeth. Bismuth and lead also form sulfides in the same manner, but these are less toxic, partly because they are less soluble. However, bismuth injections may also result in severe stomatitis.

The *actions of metal sulfides* were studied by Santesson, 1929 to 1934. *In vitro*, Hg, Bi and Cu sulfides are considerably more soluble in organ emulsions than are Pb and Zn sulfides. With hypodermic injection in rabbits, HgS is outstanding in causing violent local inflammation. Bi_2S_3 acts chiefly after absorption, on the intestines and kidneys, sometimes on the liver. CuS acts chiefly on the liver. PbS has insignificant local and distant actions. ZnS causes considerable local necrosis, but much less than HgS. Its effects on the liver and kidneys are intermediate.

The *mechanism of the salivation* is not definitely known. Since it may be diminished by atropine, it is probably partly a reflex response to the stomatitis; but this does not appear adequate. Histologic degenerative changes have been described in the parotid gland (Giani, 1913). These cannot be attributed to the concentration of the mercury in the saliva, for this is of the same order as in the blood (Lomholt found 0.05 to 0.06 mg. per 100 cc. in the saliva). The increased flow of saliva is not an immediate effect of mercury, for it is not produced acutely, as by intravenous injection. Toxic doses prevent the response to pilocarpine or stimulation of the secretory nerve (K. I. Melville).

Mercurial salivation has an interesting *history*. It was considered the effective modus operandi in syphilis, as a potent means for eliminating the materia peccans, the more the better, if not the merrier. On this theory of elimination salivation was also used in other conditions. Boerhaave and van Swieten made it a fashion so that it was taken several times a year as a general health measure, like the bleeding and purging then in vogue. A Dr. Chisholm asserted that yellow fever could be invariably cured if salivation were induced speedily, a few moments' delay in the exhibition of mercury being responsible for the deaths. Benjamin Rush advocated salivation in typhus, malaria and tuberculosis; the only trouble was that some patients, especially children, are difficult to salivate, so that he held "the greatest desideratum in medicine is to discover a mode of rendering salivation certain." John Hunter held that "no two fevers can exist in the same constitution," and that the salivation infection crowded out the venereal infection. This was the most widely received opinion at the beginning of the nineteenth century (from an inaugural dissertation of J. H. Camp, U. of Pa., 1804).

Hematopoiesis.—Small doses of mercury raise the blood count (Keyes, 1876; Schlesinger, 1884); higher doses decrease it by one and one-half to two millions (Noel Paton and others), especially in the chronic cachexia.

Metabolism.—The effects are imperfectly known, but appear to resemble those of arsenic, lead and phosphorus. Small doses, therapeutically and in animals, often cause considerable *increase of weight* (fat).

Nervous symptoms appear relatively early in the chronic poisoning, with tremor and emotional irritability. Serious mental disorders are exceptional.

The *tremors* begin as fine trembling of the fingers, interrupted by coarser movements, reinforced by excitement or intention, decreasing after the movement is started, generally ceasing during sleep except in advanced cases. They increase in intensity and extent, involving first the face, then the entire body, interfering with muscular control. The *emotional changes* (*erethismus mercurialis*) begin with lassitude, fatigue and nervousness, and progress to mental irritability and excitability and restlessness, insomnia, headache, diminished mental ability and a curious timidity, self-consciousness and embarrassment.

Calomel as Cathartic and Intestinal Antiseptic.—Mercury compounds produce intestinal irritation and therefore catharsis; but with the more soluble salts these effects are generally too violent. Calomel, the mercurous or "mild" chloride, dissolves so slowly and to so limited a degree that the irritation is mild, largely independent of the dose, and restricted mainly to the duodenum. Calomel is practically insoluble in water, and almost insoluble in the stomach and large intestine (Nemser, 1906), but in the small intestines it tends to be decomposed by the alkaline reaction of the pancreatic juice, bile and intestinal juice into mercury and mercuric oxide, and the latter dissolves slowly in the presence of proteins (T. W. Schaefer, 1910). This dissolved mercuric salt irritates the intestines to increased peristalsis and diminishes the absorption of fluid (Fleckseder, 1912). Indeed, Thiry-Vella experiments on dogs show that there is considerable secretion of fluid, some mucus, but no ferments (Sawitsch, 1926; also with metallic mercury). Radiologic examinations show that generally both small and large intestines are stimulated (Meyer, Betz and Gebhardt, 1912); but if the conditions are not favorable for solution, or with small doses, all the dissolved mercury may have been absorbed before the colon is reached, and the duodenal contents may be propelled into the colon without evacuation. Ordinarily, calomel produces dark-green semisolid stools in ten to twelve hours. The irritation is generally so mild that calomel may be used even in enteritis; but some patients appear to be hypersusceptible, and respond with marked griping and tenesmus. These also result from excessive doses. The catharsis is checked by opium or atropine. It is not influenced by the presence or absence of bile (Valeri, 1909). The *green color of the stools* is due to biliverdin. Numerous investigations with biliary fistulas have shown that calomel does not increase the flow of bile (Okada, 1915); but the antiseptic action of the dissolved mercury, and the rapid propulsion of the intestinal contents, prevent the ordinary destruction of the bile pigments. This may also be demonstrated *in vitro* (references, von Oettingen and Sollmann, 1926). Mercuric chloride and other oxidizing agents render bile more green, *in vitro*, by the oxidation of bilirubin to green and blue derivatives. The degree of this color change is a convenient index of oxidizing power (von Oettingen and Sollmann, 1927). The antiseptic action in the intestines is reflected by decrease of the urinary indoxyl. Larger doses of calomel may favor bacterial growth by diminishing intestinal resistance. Calomel is commonly used as a cathartic adjuvant to anthelmintics, but in itself is quite ineffective against the worms (Hall and Foster). The *dosage* is relatively unimportant, because the excess is usually expelled before it is dissolved. It is customary to give either a single dose of 0.125 to 0.5 Gm. (2 to 7 grains); or fractional doses of 15 mg. (¼ grain) every hour until 0.15 Gm. (2½ grains) have been taken. The divided doses insure better solution, because they are spread over a large surface, and because there is more opportunity for the coincidence of calomel and alkalinity. Formerly much larger doses were used, but they are superfluous; while usually harmless, they may become dangerous should conditions become exceptionally favorable to absorption. Calomel is not suited for long-continued use on account of its systemic actions. These may also be produced by a large single dose, if it is not expelled in the usual time. It is, therefore, advisable to follow the calomel in six hours by a saline; or it may be mixed with Resin of Podophyllum (5 mg.; 1/12 grain). Calomel should not be prescribed with iodides, nor mixed with alkalies or with many reducing or oxidizing agents.

Interaction of Calomel and Salt.—Mialhe attributed the solution of calomel to interaction with sodium chloride, forming mercury and mercuric chloride and complex double salts. Similar reactions were claimed by Joly to occur with hydrochloric and citric acids, alkalis, carbonates and sugar. The amount dissolved would be small (at most 1 to 4 mg. from 0.5 Gm. of calomel). However, mercuric chloride could not exist as such in the alkaline intestine, and the chloride can therefore not be made responsible for the solution of calomel (as was suggested, *f. i.*, by Carracido, 1906). Iodides, bromides, thiocyanates, thiosulfates, and the like, dissolve larger quantities of calomel. *Protein* (egg albumin) is distinctly solvent for calomel, and this is increased materially by sodium iodide, thiocyanate, bicarbonate and bromide, in descending order; not by chlorate, chloride, citrate or saccharose. In the absence of protein, calomel is not dissolved by moderate concentrations of any of these substances, although they may produce reduction or other changes (Sollmann).

Mercurial Diuresis.—Suitable doses of all mercury compounds increase the urine flow, especially in the presence of edema, by inhibiting the water absorption in the renal tubules. They are used to remove edema fluid in congestive heart failure, nephrosis, and hepatic cirrhosis, and have largely displaced other diuretics. They are contraindicated in acute renal disease and in advanced chronic nephrosis. Mercurial diuresis also causes marked and persistent lowering of the abnormally high venous and cerebrospinal fluid pressure of congestive heart failure (Volini and Levitt, 1940). The firm organic mercury compounds mersalyl (salyrgan), mercurophylline (mercupurin) and novasurol, which are soluble in water, practically nonirritant and ordinarily not toxic in the clinical dosage, are used intramuscularly and intravenously in preference to the older calomel, which causes objectionable diarrhea and is reliable, because of the uncertain absorption. Their activity is increased by rendering the urine acid; theophylline or theobromine is generally added to promote absorption and decrease irritation. The diuresis starts within three hours after the intramuscular or intravenous injection, reaches its peak in six to eight hours, and often continues into the next day, even after the visible edema has disappeared. During the first day, the urine volume may reach 4 or 5 liters, and sometimes 8 or 9 liters. (In *normal individuals*, the peak is reached within one or two hours, and the diuresis lasts only during the active excretion of the mercury. The median increase over the normal urine output on the day of injection is between 200 and 400 cc.; Sollmann, Mellon Lecture, 1931.) Patients have received over 600 injections of mersalyl and mercurophylline in the course of several years without evidence of damage and with continued diuretic response (M. Friedenson, 1944). However, the margin to toxicity is not wide, and the dosage should not be increased (B. J. Johnstone and Keith, 1928). Mercurial diuresis has little or no effect on *localized inflammatory edemas* (hydrothorax, pericardial effusion, tuberculous peritonitis).

Renal Damage.—Larger doses of all mercurial diuretics cause tubular nephritis, especially when the injections are frequently repeated (Lazarus-Barlow, 1928; Johnstone and Keith, 1928; Möller, 1930; Crittenden, 1932).

The failure to obtain diuresis on injection of mercuric chloride into the renal artery (Melville and Stehle, 1928) is probably due to the difficulty of keeping the concentration below the nephritic level.

Historical.—Mercurial diuresis appears to have been first recorded by J. D. Schlichting, 1741 (Proksch, 1895), and calomel was used as diuretic in cardiac dropsies by physicians in the latter half of the eighteenth century, *f. i.*, by Alex. Munro. It fell into neglect, however, and was practically rediscovered by Jendrassik in 1886–1891. Novasurol was originally introduced by Zieler, 1917, as an antisyphilitic. Its diuretic effect was described by Saxl and Heilig, 1920. References to the literature are given by Rowntree *et al.*, 1925. Salyrgan was introduced in 1924 by F. Brunn and by E. Bernheim; mercupurin by von Issekutz and von Vegh, 1928.

The *mechanism of the diuretic action* is renal, as proved by Goedert, 1928: Transplanting the kidney of a novasurol-treated dog into the neck of a normal dog, he found that the novasurol kidney excreted much more urine than the dog's own kidney; conversely, a normal kidney transplanted into a novasurol dog excreted much less than the dog's own kidneys, which had been exposed to the novasurol. Improved renal circulation is not an essential factor, for the diuresis does not go parallel to the changes in the kidney volume (primary decrease, followed by increase; Möller; W. E. Reed). Creatinine and urea clearance tests fail to show any increase of glomerular filtration, but do indicate *decreased tubular reabsorption* of water; and this is the only mechanism that has been established for the mercurial diuresis (H. Blumgart *et al.*, 1934). Rapid intravenous injection of dextrose after mercuric chloride may bring the urine volume up to the hypothetical rate of glomerular filtration (R. L. Stehle and Melville, 1943). Mercurial diuresis starts one or two hours after intravenous, two to four hours after intramuscular, injection of the organic mercurial diuretic. The diuresis is not preceded by increase of water or chloride content of the plasma, so that there is no "mobilization of tissue fluid." During the diuresis, the changes of plasma and blood volume are inconstant (Swigert and Fitz, 1940). In patients with congestive heart failure the decrease of plasma volume is roughly equal to the diuresis (D. B. Calvin *et al.*, 1940). The blood plasma concentration may increase through the loss of fluid, but the diuresis continues, nevertheless (Cipriani *et al.*, 1927; H. L. Hansen *et al.*, 1931; H. L. Schmitz, 1933; A. H. Bryan *et al.*, 1935). The injection of normal saline, which gives little diuresis in normal animals, increases the salyrgan diuresis (Möller). The increased output of the kidney involves the water and still more the sodium chloride (the latter even when diuresis fails). K and Ca are also increased. The excretion of urea, glucose, phosphate or ammonium is but little affected (Melville and Stehle, 1927, 1928; Blumgart *et al.*, 1934). The *oxygen consumption* of blood-perfused kidneys is increased by mercurial diuretics (Gremels, 1929). H. N. Wright and Bieter, 1930, reported changes in the *ultramicroscopic picture of the blood*, pointing to flocculation phenomena, which might entail diminished water affinity; but this is probably unimportant, since the flow of thoracic lymph is not increased (Yanagawa, 1916; Loria, 1912).

Synergisms and Antagonisms.—Mercurial diuresis is markedly increased by *acidification* of the urine, which may perhaps increase the ionization of the mercury. Administration of *bile salts* and their derivatives, decholine and dehydrocholate, increase mercurial diuresis (Engel and Epstein, 1931; Marengo and Massimello, 1935), and deflection of the bile by a biliary fistula prevents the diuretic response (Claussen, 1932). The mechanism is not understood. Mercurial diuresis counteracts *pituitary antidiuresis*, relieving the hydremia and oliguria. The antagonism is mutual (W. Raab, 1929). Mercurial diuresis may be suppressed by large doses of atropine (Fleckseder), ether or morphine (Schargorodsky, 1911). In *diabetes mellitus*, salyrgan produces a temporary retention of sugar, as also in phlorhizin glycosuria (Bix and Wechsler, 1931).

Mercurial diuresis is checked by certain thiols, especially by BAL (C. A. Handley and LaForge, 1947).

Toxic reactions occur occasionally with all mercurial diuretics. They take several distinct forms (review, A. C. De Graff and Nadler, 1942).

(1) *Sudden death during* or very shortly after intravenous, not after intramuscular, injection, attributable to ventricular fibrillation, probably from direct mercurial injury of the heart (J. Wexler and Ellis, 1944; L. F. Volini *et al.*, 1945). These are very few in relation to the total number of administrations. Most of the reports have been with mercupurin, but fatalities may occur with any of the mercurials. They are unpredictable; some of the patients had reactions from previous injections (G. Brown *et al.*, 1942), but the greater number had tolerated former injections without toxic symptoms.

(2) *Excessive chloride loss*, from the diuresis and not directly related to mercury, may produce the syndrome of acute chloride depletion; muscle pains, weakness,

apathy, delirium, occasionally coma. This may occur before the edema disappears. There is little if any change in the sodium and calcium level of the plasma. It has been suggested (but not proved) that the dehydration may mobilize toxic concentrations of tissue-bound digitalis in patients receiving this drug.

Tetany has occurred repeatedly in patients with low calcium levels of the blood, and was relieved by calcium administration. It appeared to be due to electrolyte imbalance, but set in before the diuresis (F. A. Marshall, 1947).

(3) *Toxicities of the ordinary mercurial types* may occur, but are rare. They are chiefly gastro-intestinal (stomatitis, salivation, hemorrhagic colitis); renal (degeneration of the tubular epithelium); cutaneous eruptions (A. Burrows and Stokes, 1945); chills and fever. Intramuscular injections may cause focal abscesses.

Toxic Effects on Animals.—The acute intravenous toxicity of the organic mercurial diuretics is fairly high. The fatal dosage of mersalyl for cats corresponds to about 15 mg. of Hg per Kg. of body weight, the same as for mercuric chloride. That of mercurin is equivalent to 30 mg. It is not materially affected by dilution of the solution or speed of injection (W. Modell and Krop, 1944). On the basis of weight, the toxicity in cats is greatest with esidrome, then, in descending order, mersalyl, mercurin, mercurophylline, mersalyltheophylline (A. C. De Graff and Lehman, 1942). Combination with *theophylline* decreases the toxicity of mersalyl to about half; it has no effect on mercuric chloride or mercurin (W. Modell and Krop). The acute deaths are due to *ventricular fibrillation*, following on changes of intraventricular conduction, and often preceded by tachycardia. It is not prevented by atropine (De Graff and Lehman, 1942). Ventricular fibrillation resulting from mercuric chloride injection into dogs was described by Salant and Kleitman, 1922, and D. E. Jackson, 1926. I. Pines *et al.*, 1944, report that the ventricular fibrillation is prevented by addition of 0.5 cc. of 20 per cent magnesium sulfate, so as to survive seven times the fatal dose.

R. A. Lehman, 1947, reports that the severity of electrocardiogram changes in cats decreases in the order of mercuric chloride, salyrgan-theophylline, mercuzanthin, and mercuhydrin (least).

Coagulation of the blood is markedly accelerated by intramuscular or intravenous injection of mercurial diuretics (not by theophylline, caffeine or theobromine without mercury). This may be a factor in the sudden deaths. The prothrombin and antithrombin times are shortened; the blood fibrinogen is increased (D. I. Macht, 1946).

Sublethal Effects on Animals.—With single intravenous injections of mersalyl into rabbits, 2 mg. per Kg. have no diuretic effect; 5 mg. give moderate diuresis; 6 to 7 mg., marked diuresis, albuminuria and acute tubular nephritis, which becomes chronic; 15 to 30 mg. produce anuria, complete necrosis of the tubules, and death in about ten days; with intermediate doses, the chronic nephritis terminates fatally in about three weeks. Dogs are rather less injured, so that 6 mg. per Kg. produce marked diuresis without albuminuria. The diuresis follows the same course as clinically, reaching its peak in about two hours and lasting about two hours. Novasurol is more toxic than mersalyl (Johnstone, 1931; Melville and Stehle, 1927; Möller, 1930). Lazarus-Barlow, 1928, considered cloudy swelling of the liver cells as the chief lesion. The addition of mersalyl to intramuscular injections of procaine, strychnine, picrotoxin and other *convulsants* materially diminishes their effect (R. Beutner, Landay and Lilberman, 1940).

Excised Organs.—The frog heart is weakened and arrested in diastole by salyrgan, 1:10,000. Excised turtle heart is depressed (R. L. Johnston, 1941). Perfused vessels are constricted by 1:25,000. Skeletal muscles go into fibrillary twitchings (Möller, 1930).

Comparison of Different Mercury Preparations.—Fourneau and Melville, 1931, found all the mercuric compounds examined by them to be diuretic, with quantitative differences related to the chemical structure. Clinically, also, the diuretic response is practically equal, but the effective dosage varies greatly, especially if it is judged by the concentration of mercury in the urine. For a given mercury preparation, the urine volume and its concentration of mercury run fairly parallel; but the concentration for the organic mercurials is about a thousand times higher than that of the inorganic, suggesting that the organic compounds are not directly diuretic, but act through dissociation of small amounts of inorganic mercury (T. Sollmann *et al.*, 1930). With the chloride excretion in dogs as criterion, mersalyl is about half as potent as mercurophylline (C. C. Roby and Pfeiffer, 1942).

The administration of organic mercurial diuretics is usually by intramuscular injection. Intravenous injection carries some risk; oral and rectal administration act more slowly, but may be used in ambulatory patients. The *intramuscular injections* produce some irritation. This is diminished (but not eliminated) by adding 5 per cent of theophylline to the 10 per cent solution of the mercurial. It acts as a buffer, materially hastens absorption and so increases the diuretic response. The amount of theophylline is too small to exert a direct diuretic action (A. C. De Graff *et al.*, 1938). *Intravenous injection* may be justified when the intramuscular is not absorbed sufficiently fast or if it produces excessive irritation. The total diuretic response is about equal to the same dose intramuscularly.

The efficiency can be materially increased by the administration of full doses of *acidifying salts* (N. M. Keith *et al.*, 1925; Modell, 1944), ammonium chloride, 6 to 10 Gm. per day, for a day or two days before a mercurial is injected. Smaller doses are ineffective. Alkalizing salts diminish mercurial diuresis (Hayman, 1936). The mechanism is not clear, but the acidification may help to liberate mercury ions in the renal tubules.

The clinical dosage is practically the same for the 10 per cent solutions of all these organic mercurial diuretics, intramuscularly and intravenously. The Injection Solutions contain, per cubic centimeter, 0.1 Gm. of the compound, corresponding to about 0.04 Gm. of Hg., with or without theophylline, 0.05 Gm. Injections of 0.5 to 2 cc. are made at intervals of three to five days. The first intravenous injection should not exceed 0.5 cc. to test for special susceptibility. The optimal dosage for continued use, as in congestive heart failure, should be adjusted by the change of weight. Smaller doses are relatively more effective than large; for instance, 2 cc. by vein is only 25 per cent more potent than 1 cc.; two doses of 1 cc. per week produce 20 per cent more weight loss than a single 2 cc. dose. Ammonium chloride increases the weight loss about 15 per cent (W. Modell, 1944).

Rectal suppositories of 0.5 Gm. of Mercurin (containing 0.2 Gm. of mercury) give diuresis approximately equal to that obtained by intravenous injection. They are administered in the morning, after a cleansing enema, repeated at three to five day intervals as needed. This causes some local irritation, generally only burning, rarely inflammation visible with the proctoscope; but it should not be used in case of diarrhea, ulceration, fissure, or congestion. Salyrgan suppositories, 0.4 Gm., are also effective, but cause much more irritation, sometimes even ulceration (De Graff *et al.*, 1939). *Calomel* has been administered orally as a diuretic in doses of 0.2 Gm. four or five times a day, until slight stomatitis appears, the bowels being meanwhile regulated with an opiate.

PREPARATIONS.—*Merbaphen* (*Novasurol*), the double salt of sodium mercuric chlorphenyloxyacetate with diethyl-barbituric acid (barbital), contains not less than 33 and not more than 34.5 per cent of Hg. A white crystalline powder. Sol. in cold water, the solution being slightly alkaline. Dose, 0.15 Gm., intramuscularly. This appears to be the most toxic and most irritant of the organic mercurial diuretics, and has only historic interest.

Mercurin, N.N.R. (*Novurit*), a complex organic Hg compound, derived from salyrgan by replacing the benzene ring with a camphoric nucleus, contains 40 per cent Hg. Dose, as rectal suppositories, 0.5 Gm., mornings, at intervals of three to five days. Local irritation indicates discontinuance. ***Mercurophylline Injection**, U.S.P., *Mercuzanthin, Mercupurin;* a watery solution of mercurin with theophylline. Usual sizes of ampul, 0.1 and 0.2 Gm. of the mercury compound with 40 or 80 mg. of theophylline in 1 cc. Average dose, 0.1 Gm. intramuscularly. Mercurophylline may also be used orally (Batterman *et al.*, 1944).

Mersalyl, U.S.P., *Salyrgan*, the sodium salt of salicylalbylamide-orthoacetic acid, containing about 40 per cent of Hg. A crystalline powder, gradually decomposed by light; freely soluble in water. Administered as ***Mersalyl and Theophylline Injection**, U.S.P.; 100 mg. of mersalyl and 50 mg. of theophylline per cubic centimeter. Average dose, 0.2 Gm. of mersalyl. *Mersalyl and Theophylline Enteric Tablets*, N.N.R., each containing 80 mg. of mersalyl; *dose*, 2 tablets after breakfast, repeated in four or five days.

Meralluride, N.N.R. (*Mercuhydrin*), contains equimolecular quantities of a mercury compound of allylsuccinyl urea, and of theophylline, with about 32 per cent of Hg.

The Place of Mercury in the Treatment of Syphilis.—Syphilis can be checked by mercury, but more slowly than by arsphenamine or even by bismuth. The treponemas disappear from the lesions, and the symptoms subside completely, at least in the early stage. As in other protozoan infections, however, and in a rather higher degree, the invasion recurs unless the treatment is continued for some time. The permanent clinical cure for syphilis requires continuous energetic medication during the greater part of two years. This is accomplished by the alternation of several remedies to avoid the chronic poisoning which follows the unintermittent intensive use of a single metal. When mercury was the only antisyphilitic drug, it was pushed to actual poisoning, and then stopped completely, or it was administered continuously in harmless but ineffective dosage, until Fournier introduced the "intermittent treatment," alternating fairly intensive "courses" of active medication with "rest periods" of about equal duration. This system was transferred to the arsphenamines, whose continued use may become even more toxic than that of mercury. The alternation of the two drugs gives this "rest" to the patient, without giving any respite to the parasites. It avoids the cumulative intoxication, but enhances the therapeutic effect, partly by permitting higher dosage, and probably also by attacking the parasites from several angles. Arsphenamine and mercury or bismuth are therefore given in alternating courses of four to six weeks' duration, stressing at first the arsphenamine, because of its more rapid action; and later the "heavy metals," which can be used more cautiously, and the effects of which appear to be more thorough and more persistent. Bismuth is intermediate between mercury and arsphenamine in rapidity and perhaps in kind; it has the practical advantage of causing less pain, and is less liable to serious stomatitis. The relatively high toxicity of mercury limits the use of effective quantities, and doses that are ordinarily well tolerated may in some cases prove toxic. For these reasons, bismuth has largely displaced mercury. Several other metals are also more or less antisyphilitic (Levaditi; H. Schlossberger, 1931; von Oettingen), but appear practically inferior. A number were tried during the antimercurial agitation in the early nineteenth century, but as they are less effective than mercury, they were properly abandoned. The chemotherapy of syphilis, including mercury, is more or less useful in all stages of the disease, except against the late sclerotic lesions. As with other protozoan infections, the response is the more satisfactory, the earlier adequate treatment is started. When the disease has become thoroughly established by the neglect of proper treatment, it is much more resistant. This holds also for experimental syphilis in mice (Schlossberger, 1931).

Contraindications to Mercury.—Caution should be exercised with weak or anemic individuals, with albuminuria, during digestive derangements, and with diseases of the mouth or teeth. Pregnancy is not considered a contraindication. It is safer to begin treatment with small doses, since some patients are hypersusceptible.

Antisyphilitic prophylaxis by calomel ointment has a questionable status. It was believed that it often prevents the primary and secondary lesions, if it is applied locally before the treponema has penetrated, *i. e.*, within four or at most eight hours after exposure; the site of the suspected infection being cleansed with soap and dressed with an ointment containing 33 per cent of calomel or 0.3 per cent of sublimate ("Neisser-Siebert Ointment"). However, Schlossberger, 1931, found that the prophylactics prevent the dissemination of spirochetes through the scarified skin of mice only if the application of the agents preceded that of the treponema; they were totally ineffective if applied even immediately after the treponema. This suggests that clinical prophylaxis does no real good, but rather harm by preventing the recognition of infection. It is conceded clinically that mercury should not be used locally, if twelve hours have elapsed.

Historical.—Mercurial inunctions were introduced by the Arabian physicians, about 1000 A.D., against chronic skin diseases, and became widely known through the popular medieval textbook, the "Canon" of Avicenna (980 to 1036). They were pushed to intensive salivation, to "depurate the humors." There are those who contend that the conditions which responded were syphilis, which had not yet been differentiated from lepra, variola, typhus and other eruptive diseases (Sudhoff, 1926; in contrast to the traditional view that syphilis was imported from America by the expeditions of Columbus). When syphilis was definitely recognized in 1495, it was at once met by this intensive mercurial treatment, through inunction and other methods of administration (reviews of the history of mercury in syphilis may be found, among others, in J. K. Proksch, 1895; Haeser, 1882; and in the Mellon Lecture of Sollmann, 1930). Until the discovery of arsphenamine in 1905, mercury remained, with some vicissitudes, the only effective treatment of syphilis. Originally, the administration was pushed energetically until profuse salivation occurred, so that the improvement must have been prompt and striking. The treatment was stopped, however, as soon as the secondary lesions were healed, since the latent course of the tertiary syphilis was not understood. When this was realized, the therapy had already been made less energetic to avoid the risks of severe stomatitis. Between the inadequate dosage and deficient persistence of treatment, the results were often imperfect. As this was difficult to recognize by the course of the symptoms alone, little progress was made until the recognition of the Treponema pallidum and the Wassermann reaction furnished more definite criteria, and the transfer of the disease to animals made experimental controls possible. The latter, however, have chiefly qualitative value; results with allied protozoan affections of animals (spirillosis, trypanosomiasis) do not go parallel with antisyphilitic efficiency. The prejudice against mercury led to the introduction of a number of vegetable "alteratives," such as guaiac, echinacea, phytolacca, iris, sarsaparilla, and others, as *vegetable antisyphilitics*, but their uselessness is attested even by eclectic practitioners (Hilton, 1909). *Mercury in tuberculosis* was advised by B. L. Wright, but Hartz, 1910, found the ultimate results detrimental and never beneficial.

The **effects of mercury on syphilis** appear analogous to those of arsphenamine and bismuth, but are rather slow and progressive: suppression or rather great diminution of the treponemas in the lesions and presumably in the body; clearance of the superficial secondary manifestations, the eruptions, mucous patches, and so forth; and gradual disappearance of the positive serologic reactions. The tertiary lesions are checked or arrested. If treatment is stopped too early, the disease again becomes active and perhaps more resistant to therapy. Sufficiently prolonged treatment with mercury alone may produce permanent cure in rabbits (Kolle), but it is not safe to rely upon it clinically. The *theories of the mechanism* of the antisyphilitic action are not supported by adequate evidence.

They include direct toxicity to the parasites (Neisser), stimulation of the production of immune substances (Finger), increased resistance by other factors, increased susceptibility of the parasites to the protective mechanisms, and combinations of these factors. Mercury solutions are directly fatal to the treponema *in vitro*, and also in the local prophylactic treatment; but the concentration of mercury in the blood, probably not over 1 mg. per liter, appears far too low for this effect. The *explanation of the relapses is also hypothetical*, as with other protozoan infections. It may be assumed that the main mass of the parasites is destroyed in the active treatment, but some escape, probably by assuming a less active but more resistant form; perhaps also by being in protected situations, such as occluded capillaries or impermeable tissues. The multiplication of these surviving treponemas is checked by the treatment, and they eventually succumb; but if the checks are prematurely withdrawn and the factors of body resistance weakened, they reawaken to activity. The increased difficulty of treatment may be due to persistent foci of resistant forms.

Objectives in Mercury Administration.—The relapses start rather promptly after medication is discontinued, and when there are still considerable quantities of mercury retained in the tissues. It is therefore evident that the stored tissue mercury is not antisyphilitic; indeed, its slow excretion indicates that it is in an insoluble and therefore inactive form, and the action must be due to dissolved mercury. This is in diffusion balance between the tissues and blood, and through the latter it is reflected in the urinary excretion. The therapeutic effects are presumably proportional to the concentration of active mercury in the blood. With all inorganic mercury compounds, the urinary concentration of mercury is between 0.4 and 3 mg. (median, 0.65) per liter, or 0.5 and 2 mg. per day, when the therapeutic effects develop; and the subtoxic phenomena, the stomatitis, may appear about the same level. Compounds with organically combined mercury (salyrgan and novasurol) give considerably higher concentrations, as reflected by the higher urinary excretion; from 8 to 40 mg. of Hg per day; but they have little antisyphilitic action and do not produce stomatitis; presumably their mercury is too firmly bound to be active, and the excretion curve indicates that the high concentration is of short duration. The slowness with which therapeutic effects develop even with the active preparations indicates that the Hg concentration must be maintained for some time; however, the gradual effects depend in part on the methods of administration, by which the amount of daily absorption increases slowly, partly because this is inherent in the methods, and partly because it is desired to test the tolerance of the patient.

The *objectives of mercurial treatment* therefore are to furnish a continuous supply of mercury in active form, at sufficiently high concentration, raising this gradually so as not to exceed the tolerance of the patient. In principle this may be accomplished by frequently repeated dosage with easily absorbable mercury, or by the establishment of depots of sparingly soluble mercury for continuous absorption. In fact, however, all clinical methods involve deposition, and the effects are therefore more or less continuous and outlast the administration, as may be recognized by the slow descent of the excretion curve, which remains high for a week or two after the course is ended. With inunctions a store of metallic mercury accumulates in the ducts of the skin; with oral administration, the insoluble or precipitated compounds must be retained between the villi. Intramuscular injections of sparingly soluble compounds, metallic mercury, calomel, salicylate, generally in oily suspension, form depots among the muscles. These cause irritation, however, and become walled off by fibrous tissue, so that a part of the mercury remains unabsorbed for weeks, sometimes indefinitely, as shown by radiography (Cole, Littmann and Sollmann, 1920). Watery solutions of mercury salts, for instance sodium mercuric iodide, are absorbed more rapidly and more smoothly from intramuscular injections, but as the sodium iodide diffuses rapidly, the mercury reacts with the proteins to form precipitation depots. Even intravenous injections are deposited, since they tend to flocculate with protein and are caught in the reticulo-endothelial system. This "depot" mercury must be distinguished from the "stored" mercury that has been absorbed in diffusible form, penetrated into the cells, and been fixed there. The long-continued excretion of minute traces of mercury shows that this is also gradually mobilized, at least with the death of the cells; but its concentration is too low for any appreciable action.

Clinical Excretion Studies.—The course of the urinary excretion of mercury indicates how far the objectives are fulfilled by the clinical administration. The fecal excretion is less useful for this purpose, because it involves other factors. It is indispensable for determining the total excretion, and through this the quantity of mercury retained in the body. In this, the amounts excreted by minor channels must be neglected; the retained mercury includes that which has never been absorbed as well as that which has been deposited in the tissues. The excretion data gathered by several investigators (Buergi, 1906; Buchtala, 1913; Lomholt, 1920; Cole, Schreiber, Sollmann and associates, 1926 to 1931) agree in their general features. The present summary is based mainly on the figures of the American work. The course of the urinary mercury excretion, and therefore the blood concentration and therapeutic action, ranges in the different methods from (1) periodic and completely remittent; through (2) incompletely remittent and therefore cumulative; to (3) continuous progressively increasing excretion. The (1) *periodic and completely remittent type* obtains for all intravenous injections, organic, ionizable and colloidal suspensions. The excretion rises and declines acutely, reaching its maximum in one to two hours, and ceasing practically in eight to twenty-four hours. This type applies also to intramuscular injection of several nonprecipitating organic compounds (novasurol, flumerin; with salyrgan the decline is not quite so acute, but it attains approximate zero in the clinical intervals). The (2) *incompletely remittent cumulative excretion* is illustrated by the salicylate suspended in oil: The excretion rises and declines promptly, as in the periodic type, but the decline is incomplete, so that the excretion of the successive injections becomes superimposed, cumulative and even somewhat potentiated. The (3) *continuous progressive excretion* is obtained when the absorption is nearly continuous, so that there is no opportunity for remission. This occurs when depots are established by inunction, and by intramuscular injection of difficultly soluble preparations, gray oil or calomel. The excretion in the after-period declines slowly, so that the therapeutic level is maintained for a week or two after the end of the course. Transitions between types (2) and (3) are furnished by oral administration, and by daily intramuscular injections of ionizable compounds, sodium mercuric iodide or bromide.

Quantitative comparisons of the various methods of administration should be based upon the median of a number of patients; for while the general features of the course of excretion are fairly uniform for a given method, the amount of the excretion varies considerably, especially with methods that involve absorption (Sollmann, Schreiber, Cole *et al.*, 1935). In view of the importance of maintained concentration, the therapeutic efficiency is probably best reflected by the daily urinary excretion, at the end of the fourth week, remembering that the effective level is between 0.5 and 2.5 mg. of active mercury per day. The level at the end of the first week reflects the speed of action. The urinary level attained during the period of maximal excretion may be higher than the level at the end of four weeks. The total cumulative excretion, *i. e.*, the total amount excreted in four weeks, is interesting chiefly in comparison to the amount of retained mercury. The latter is useless and potentially harmful.

The *fecal excretion* is variable and runs a more irregular course, partly because the intestinal contents are not necessarily expelled on the day when they are formed; and as they are not formed by filtration as the urine, their relation to the plasma concentration is less direct. Some is probably excreted directly into the intestines, but most through the bile, involving the activity and affinity of the hepatic cells, which is much higher for some compounds, such as *flumerin*, than for others. For other injections the median ratio of fecal to urinary mercury averages about 1:5. *Excretion* by the sweat is negligible under ordinary conditions; but 900 cc. of sweat collected in an hour after pilocarpine administered during a course of mercury salicylate injections contained 0.08 mg. of mercury. *Saliva* contained in one case 0.06 in 115 cc., in another, 0.08 mg. in 150 cc. (Lomholt).

The *form of mercury in the urine* is mostly inorganic, so that this part is precipitated directly on electropositive metals (Lomholt, 1928). The late excretion (three years after chronic poisoning) was entirely in the sediment (R. Probst, 1932).

Details of Administration.—The following paragraphs aim to give the principal facts that may aid in the choice and application of the various methods and preparations. Septic conditions in the mouth, particularly about the margin of the gums, should be treated before any form of mercury is administered, and oral hygiene should be painstakingly observed, employing hydrogen peroxide as mouth wash; the patient should be frequently examined for the first signs of stomatitis.

Inunction is a very effective method of administering mercury, with a minimum of undesirable local effects; the slow intensification of absorption makes it easy to avoid serious overdosage. On the other hand, it is time-consuming, dirty and disagreeable, difficult to keep secret and the dosage is uncertain. The excretion varies in individual patients from less than half to more than twice the median. The usual technic in the United States is to rub 4 Gm. of "Strong Mercurial Ointment," U.S.P. (*i. e.*, 50 per cent), vigorously into the skin for half an hour to an hour, until it appears entirely absorbed. The "rubs" are repeated every night on a different skin area, thus increasing the absorbing surface, making the tour of the body in six nights. On the seventh night, a hot bath is substituted, and so on. The course usually lasts for four to six weeks, unless the gums become definitely tender, which may occur after ten to twenty rubs.

In Europe, the milder mercurial ointment (25 to 33 per cent) is used, probably with more vigorous friction. The tell-tale excess ointment may be sponged off with benzene (Cole, Gericke and Sollmann, 1921; Cole, Hutton and Sollmann, 1924); but this reduces the excretion to half: The daily rotation may be replaced by a single weekly administration, rubbing 30 Gm. of a 30 per cent mercurial ointment into the entire skin for an hour. Although the quantity of mercury is but two-thirds of that of the rotation system, the absorption is fully as high, and practically a week is saved in attaining the effective level (Cole, Rauschkolb *et al.*, 1929).

Historical.—The early mercurial salves contained only 5 to 13 per cent of mercury, but they were applied much more intensively, by vigorous rubbing of the entire body with 2 or 3 ounces at a time, daily or on alternate days, so that three rubs or less sufficed to produce the severe salivation considered necessary to remove the syphilitic poison. This was still the opinion and practice of Sydenham (1624 to 1689), and of Boerhaave (1668 to 1738); the latter was not content with less than 3 or 4 pints of saliva per day. The absorption was intensified by preliminary sweating and the treatment rendered more exhausting by severe dietary restrictions. A reaction against the supersalivation was started early (Almenar, 1502), and the toxic effects led to opposition to the use of mercury and the substitution of the ineffective guaiac treatment (Ulrich von Hutten, 1519); but mercury proved indispensable and notwithstanding some further protests (Chicoyneau of Montpellier, 1718), its effect remained identified with the flood of saliva until about 1820, when another antimercurial movement (A. Mathias, "The Mercurial Disease," 1810), the spread of homeopathy, the decline of the humoral theory of disease, and particularly the influence of the practical syphilologist, Ricord (1800 to 1889), led to the final recognition that salivation is not necessary to the treatment.

The *median level of urinary excretion*, with the normal technic (4 Gm. of 50 per cent ointment per day, rotation, no benzene), is as follows at the end of each week: first week, 0.12 mg.; second, 0.33 mg.; third, 0.60 mg.; fourth, 0.83 mg.; and sixth, 0.98 mg. After discontinuing, the level remains unchanged for about a week, then declines slowly and logarithmically, by about a third at the end of four weeks. The cumulative urinary excretion (the total amount excreted during the entire time) at the end of the fourth week is about 11 mg., with the normal technic; 5.4 mg., with benzene washing; and 16 mg., with massive inunctions. The fecal mercury varies widely, from a ninth to ten times the amount of the urinary. The urinary excretion figures of foreign workers average two or three times higher, presumably because of more vigorous rubbing. This and the area of skin inuncted (paralleling the quantity of ointment), and the mercury concentration of the ointment, are the more important controllable factors. The excretion is almost proportional to the concentration of the ointment. The texture of the skin is also important. Cutaneous syphilides have no significant effect; but fatal poisoning has been reported from the inunction into the open surface of a fissured eczema (Sackur, quoted by Lomholt). The ointment base has no material effect (Sollmann, Cole and Schreiber, 1935).

Manner of Absorption.—The mercury is absorbed mainly from the upper portions of the hair follicles and from the gland ducts, into which it is forced by the rubbing, and where it is gradually converted into soluble compounds. The epidermis probably does not participate in the absorption (Zwick, 1925). A variable quantity of the mercury is also conveyed by the hands, from the skin to the mouth of the patient; for instance, the ratio of fecal to urinary excretion is five times higher with inunction than with intramuscular injection (Cole *et al.*). Some absorption occurs through inhalation (Schamberg *et al.*, 1918); this has been estimated as one-fourth to one-half of the total absorption, but the data are not convincing, as they are based either on animals with a different skin structure (Juliusberg), or on the excretion of noninuncted patients in inunction wards, with their extraordinary mercury-vapor concentration, and extensive opportunity for hand contamination.

In man and animals, mercury globules can be demonstrated in the hair follicles and sebaceous ducts to about two-thirds of their depths, but only in the orifice of the sweat glands. The surface of the globules becomes dulled by the formation of oxide and in a week may have disappeared, almost completely in four weeks. No mercury is absorbed from a skin free of hair follicles and ducts, so that it does not penetrate the dry epidermis. When the skin is macerated, however, as with mercurial plasters, some absorption occurs. Mercuric chloride in 1:1000 watery solution is absorbed from the intact skin sufficiently to be demonstrated in the excreta after twenty-four hours of immersion (Fuerbringer, 1880).

The *size of the mercury globules* is probably of less importance than their fluidity. Ointments of *colloidal mercury*, which behaves as a solid, give variable, but generally smaller, absorption.

Mercury Oleate.—Mercurial ointments generally contain small quantities of mercury soap, added as oleate to aid emulsification, or formed by rancidity of the fat. This led to the suggestion that the mercury is absorbed only in this form (Menschel, 1923); but the absorption of the oleate is little better than that of metallic mercury, and the quantity is too small to be significant. The oleate is inconspicuous and has the further advantage that it does not require prolonged friction. It may be applied as an ointment, of which 15 Gm. contain 1 Gm. of mercury, as the daily dose (Sollmann, Cole and Schreiber, 1935).

Mercury plasters were attempted early, but were soon abandoned. They cause considerable local irritation; and since they do not force the mercury into the ducts, they are not reliable.

Powdery triturations were tried (with lycopodium, Unna; with clay mud, Talge, 1920), but abandoned. No excretion studies are available.

Calomel Ointments.—Very little is absorbed from the inunctions, and these have proved ineffective clinically (Cole *et al.*, 1933). The absorption from the skin of rabbits and rats was studied by Laug *et al.*, 1944.

Oral Administration.—Effective quantities of mercury are absorbed without difficulty from the ordinary therapeutic dosage, as shown by salivation as well as by the urinary excretion, which is as high as with inunctions or injections. The excretion rises progressively with continued administration, and declines rather slowly in the after-period, though somewhat faster than with inunction. Judging by the excretion, the daily dose of 0.2 Gm. of mercury with chalk, or 0.064 Gm. of mercurous iodide, would be equivalent to inunctions with 4 Gm. of 50 per cent ointment; mercuric chloride, 15 mg., would be but a fourth to a third as potent, and therefore of doubtful efficiency (Sollmann, Schreiber and Cole, 1935). The gastro-intestinal irritation is a serious disadvantage which restricts the oral administration mainly to the less soluble preparations; but these also tend to produce diarrhea and they have the further disadvantage of variable absorption, according to the solution and catharsis. The most serious disadvantage of the oral method is, however, that the patient is under less perfect control. It has therefore been largely abandoned except for newborn infants. To these mercury with chalk may be given in doses of 0.015 to 0.03 Gm. three times per day.

For adults, the oral method was used continuously: beginning with a small dose, this is increased daily by about 10 per cent, to tenderness of the gums. The dose is then reduced to one-third or one-half and continued at this point till the end of the treatment. The usual preparations are, *Yellow Mercurous Iodide* ("protoiodide"), 10 to 50 mg.; *Mercury with Chalk*, 0.05 to 0.2 Gm. (introduced by Jonathan Hutchinson); *Mercuric Chloride*, 5 to 15 mg., prescribed in solution with an excess of potassium iodide and taken in milk, to prevent corrosion. All these doses are used three times daily, after meals. The daily dosage of *calomel* for adults is from 0.05 to 0.1 Gm.; for infants, 0.01 to 0.03 Gm.

The mercuric chloride should be prescribed in solution, with an excess of potassium iodide, and administered in milk, to prevent local corrosion.

Rectal Administration.—Suppositories containing emulsified mercury have been suggested as a convenient method; but the absorption appears insignificant; the daily urinary excretion after ten days of administration was only 0.03 mg. (Cole *et al.*, 1926).

Fumigation.—The inhalation of heat-volatilized mercury, mercuric sulfide, oxide, or calomel, and so forth, is properly obsolete. The dosage is indefinite and there may be serious pulmonary irritation (Cole, Gericke and Sollmann, 1922).

Inhalation of mercury vaporized at room temperature was advocated especially by Merget, 1894, and Welander, 1900' but has not become popular, because of the uncertain dosage and of the inconvenience. It is practically devoid of local action, and effective quantities may be absorbed, as indicated by the urinary excretion of 1 to 4 mg. per day (Farup, 1901).

Intramuscular injections have the advantage that they keep the patient under frequent observation by the physician. They are therapeutically effective and avoid the conspicuousness of the inunctions and the direct gastro-intestinal irritation of the oral administration. They are painful, however, and the capricious absorption of the poorly soluble preparations may cause serious poisoning. The effective mercury compounds are so irritant that injection into the subcutaneous tissue may result in sloughing. The injections are therefore made deep into the gluteal or lumbar muscles. They generally rupture the muscle bundles and follow the nearest fascia, so that the location of the mercury is interfascial as well as intramuscular. The spreading reaches its limits within a few minutes (L. W. Shaffer, 1929). The muscle fibers in the immediate vicinity degenerate (Gruhzit, 1929). This is of no practical importance in itself, but contributes to the inflammatory reaction. The ionizable preparations cause immediate pain, which lasts some hours; it may be diminished by injecting 1 cc. of 2 per cent procaine solution through the same syringe. With the insoluble preparations, the *pain* develops later, but may last for some days; calomel is the most, gray oil the least, painful. Heat and rest give relief. Small amounts of concentrated solutions are generally less painful, because fewer nerve fibers are involved; but this also diminishes the area for absorption (Lomholt). The slow absorption of the insoluble preparations is utilized with the idea of establishing depots so that weekly injections would furnish a continuous supply of mercury. However, if the absorption is not promptly completed, *the remaining mercury becomes encapsulated* with inflammatory and fibrous tissue, and this slows absorption to an incalculable degree. Roentgenographs (Cole, Littmann and Sollmann, 1920) show that the mercury salicylate is generally absorbed within a week and calomel in two weeks; the greater part of metallic mercury suspension ("gray oil") remains unabsorbed after four weeks. The mercury that remains unabsorbed at the time of the next injection is a source of danger; for if conditions should become more favorable for absorption, the multiplication of depots may give rise to serious cumulative poisoning.

Absorption from Intramuscular Injections.—The mercury, in whatever form it is introduced, acts on the proteins to form albuminates of mercury. These are strongly chemotactic, and attract leukocytes. Some of these are killed, but others take up the mercury, especially in their nuclei, and distribute it through the body; its final fate is the same as with other methods of administration (Lombardo, 1912). The quantitative excretion is capricious.

Water-soluble ionizable compounds by intramuscular injection cause considerable pain, which is especially objectionable, since they must be made frequently. Mercuric chloride (1 cc. of 1 per cent solution) is particularly painful, and is therefore not advised. The irritation is materially diminished by conversion into the "biniodide," by adding 2 per cent of sodium iodide to a 1 per cent solution of mercuric chloride; or the sodium or potassium mercuric iodide may be used directly, as 1 per cent solution, adding 0.2 per cent of sodium iodide. In either case, 1 cc. of the 1 per cent solution is injected every day or on alternate days. Salts with organic acids (the benzoate, succinimide, oxycyanide and cyanide) have also been used. Absorption starts promptly, but the compounds form poorly soluble precipitates with proteins, and the absorption becomes slowed and incomplete. The injections must be repeated almost daily, at least every two or three days, to maintain an effective concentration. This establishes multiple depots, and the absorption rises gradually to the effective level, the median excretion curve with daily injections of the double bromide, equivalent to 5.5 mg. of mercury, being practically identical with that of the 50 per cent simple inunctions; *i. e.*, 0.4 mg. of urinary mercury at the end of the first week and about 1 mg. at the end of the fourth week. With the clinical dosage of the benzoate the median urinary mercury maintained only 0.12 mg. per day, which is probably insufficient.

Water-Soluble Nonionizing Compounds by Intramuscular Injection.—These include novasurol, salyrgan and mercurosal. The antisyphilitic action of the first two is slight and practically unreliable; the same would be expected from mercurosal. They cause little local irritation and are not toxic in the clinical dosage, nor does stomatitis develop in the course of weekly administrations. The urinary excretion curve rises rapidly to a high peak, attaining 1 to 5 mg. per hour (twenty-five to 100 times the median of the intramuscular bromide and of the four-week inunctions); it then falls promptly, becoming insignificant in eight to twelve hours, with novasurol; but salyrgan and mercurosal maintain a slight excretion. The total urinary excretion of the first day is about 12 mg., for all these compounds, *i. e.*, about fifteen times that of the four-week inunctions. The absorption is therefore rapid and fairly complete, but with mersalyl and mercurosal, a small part is absorbed more slowly. The retention in the four weeks is one-third to one-half of the quantity injected. Although this ratio is considerable, it is less than with any of the other mercury compounds.

Mercuric salicylate (for intramuscular injections) is not a simple salt, as the name would imply, but a molecular compound, with one valence of the mercury united directly to the benzene ring. It is insoluble in oil and in water, but it dissolves in the presence of various salts, including sodium chloride and proteins. It is administered as weekly injections of 1 cc. of a 10 per cent suspension in oil = 60 mg. Hg. It is effectively antisyphilitic, and may produce stomatitis, but this is rarely serious. It has the advantage of causing relatively little pain.

The urinary excretion curve suggests a sequence of organic and insoluble injections. It rises promptly in two to four hours, to a peak of 0.13 to 0.87 mg. of mercury per hour, about a sixth of the novasurol level, but ten or thirty times that of the bromide. It then declines, at first rapidly and then more slowly. The daily excretion is from 2 to 10 mg. per day, on the first day, to the median of 0.34 mg. at the end of the week; in the next two or three injections, the excretion level rises somewhat, the daily median at the end of the fourth week being 2.3 mg. About two-thirds of the mercury is retained at the end of the fourth week (Cole, Gammel *et al.*, 1929). The excretion curve indicates that a part of the compound is promptly absorbed unchanged; *i. e.*, in molecular form, and therefore inactive, and that the remainder is decomposed into poorly soluble compounds, which establish absorption depots of effective mercury.

Difficultly soluble mercury preparations by intramuscular injection have been administered suspended in oil; especially calomel, 10 per cent, 0.5 cc. weekly to 1 cc. twice weekly; and metallic mercury, finely divided, as the "gray oil" (oleum cinereum), 40 per cent, ½ cc. weekly, not to exceed five injections. Although they are highly effective (calomel also in experimental rabbit syphilis, Döhring, 1915), they have gone practically out of use because it is not possible to control their absorption; they are liable to produce excessive stomatitis, especially the gray oil, which has caused several deaths. Calomel injections also produce severe local irritation; the gray oil but little. Their absorption is slow, since they must first be converted into soluble compounds; but when the injections are repeated, the absorption from the multiple depots become cumulative and uncontrollable. The urinary excretion was studied for gray oil by Lomholt and Christianson; for calomel by Lomholt and by Buergi. It increases slowly from about 0.5 mg. per day at the end of the first week, to 2 or 3 mg. by the fourth week; but it varies considerably from day to day, indicating capricious absorption which is probably responsible for the disproportionate toxicity. The absorption is greatly increased by the administration of haloids, especially by iodide, which forms soluble mercuric salts; bromide is also dangerous, and to a less degree, excessive chloride income (F. Garcia, 1928, fatality to rats). *Mercuric sulfide* also produces local irritation and systemic toxicity, so that it must be converted into soluble, ionized compounds. It is not irritant or toxic by mouth (in rabbits; H. Niklasson and Santesson, 1926).

Intravenous injections were introduced (by Bacelli, 1892) to secure the maximal concentration of mercury in the blood and to avoid the local actions of the mercurials. However, they irritate the veins at the site of the injection and tend to produce fibrosis, which precludes the use of the vein for further injections, a rather serious matter for syphilitic patients. They also present some danger of embolism and colloidoclastic shock, at least in inexperienced hands. Urinary excretion studies indicate that the high concentration in the blood is of too brief duration to be important in chemotherapy, and that the maintained level is generally too low, even with daily injections. The excretion is incomplete, the retention at the end of the fourth week of treatment amounting to half or more for the diffusible preparations, organic and inorganic, and from 97 to 99 per cent for the colloidal. The diffusible mercury is presumably bound in the tissues and remains inactive. *The colloidal compounds* are probably enmeshed in the reticular endothelium, forming depots from which active mercury is absorbed and circulated for long periods; but the absorption is capricious and uncontrollable. The mercurial dye flumerin occupies a peculiar position and probably produces flocculation reactions.

Ionizable mercuric salts, mercuric chloride, oxycyanide, benzoate or the double iodide have been administered by vein, generally in 1 per cent solution, 1 to 3 cc. daily or every second day, using a glass syringe and platinum-iridium needle (Crume, 1908). With mercuric chloride, it is advisable to add 3 per cent of sodium chloride to the solution. Similar injections have been tried in puerperal infections and other septicemias, influenza, and so forth (Barsony, 1909). Vecki, 1918, endorses this use, but reports severe poisoning, exceptionally from 3 mg. The therapeutic results in syphilis are probably not so good as with other methods of administration, certainly no better (A. Strickler, 1923). With the oxycyanide, 10 mg. = 8.5 mg. of mercury, twice a week for four weeks, the daily urinary excretion was 0.02 mg. at the end of the first week and 0.1 mg. in the fourth week, distinctly too low for therapeutic results. The excretion rose to a peak of 0.12 mg. per hour in one or two hours after each injection, which is about ten times the average level after intramuscular injection of the sodium mercuric bromide; but it fell rapidly and was insignificant by the next day.

Organic Mercury Compounds by Intravenous Injection.—The urinary excretion of novasurol, salyrgan and mercurosal rises in one to two hours to a high peak, and declines promptly, leaving an insignificant level within eight hours after the injection. With injections of 1 cc. of the 10 per cent novasurol and salyrgan solutions (= 34 and 38 mg. of mercury), weekly, and of 0.1 Gm. of mercurosal (= 34 mg. of mercury) every second and third day, the hourly urinary excretion at the peak was 4 to 8, 10 to 27, and 21 to 30 mg., for the respective compounds. At the end of the first week, the median daily urinary excretion had fallen to 0.03, 0.04 and 0.3 mg.; these levels would be quite ineffective even if they represented active mercury. Mersalyl did not cause any untoward symptoms; but novasurol and mercurosal produced bloody diarrhea in some of the patients. Novasurol and salyrgan have been injected clinically with arsphenamine, which would disguise their inefficiency.

Flumerin, **N.N.R., is derived from sodium fluorescein, with the mercury united to the benzene ring. Like other dyes, it tends to form colloidal adsorption products with proteins. Promising results were reported in experimental syphilis of rabbits; in man, 3 mg. per Kg. have been injected every second day, with gradual therapeutic effect (White, Hill, Moore and Young, 1922), but probably not better than with ordinary mercurial treatment. This dosage produces subtoxic phenomena in a considerable proportion of patients (stomatitis in a third, renal irritation in a fifth, gastro-intestinal disturbance in a fifteenth of the cases); but these are temporary and generally not dangerous. The *fecal excretion* surpasses by far all other mercurials that have been studied, attaining 1 mg. on the day of the injection, indicating a biliary excretion of the unchanged compound. The *urinary* excretion is intermediate between the organic and the colloidal compounds, inclining rather more to the latter. It starts promptly, attaining the fairly high peak of 0.45 mg. per hour, in the second hour. The daily excretion is 2.6 mg. on the first day, 0.4 mg. on the second and 0.25** at the end of the week. The latter is still below the therapeutic level, but it is about five times as much as with the organic compounds, indicating the deposition of colloidal depots, probably in the liver.

Spinal injection of mercurialized serum was introduced by Byrnes, 1914, and endorsed by Ireland and Wilson, 1915, against cerebrospinal syphilis, as being about equally successful and safe as the Swift-Ellis serum, but it did not become established. Swift, 1916, believed that repeated injections of mercurialized horse serum render the membranes hypersensitive and tend to produce chronic meningitis.

Mercury Mobilization by Iodide and Other Halogen Salts.—The impression prevails clinically that the administration of iodide mobilizes the mercury stored in the body from previous treatments. This has not been investigated adequately by modern methods, but Ludwig, 1929, claimed that a double iodide is formed which breaks down the mercury-protein compound in the tissues; Young and Taylor, 1929, believed that mercury is deposited in the bones, similarly to lead, and as the latter is mobilized by iodide, this might also happen with mercury. Garcia, 1928, reported that administration of halogen salts increased the toxicity of subcutaneous injections of insoluble mercury salts in rats, by accelerating absorption; the order of efficiency being I > Br. > Cl.

PREPARATIONS—METALLIC MERCURY.—*Mercury with Chalk,* U.S.P. (Hydrargyrum cum Creta; Gray Powder), contains about 38 per cent Hg, dispersed in chalk. A light gray, rather damp, sweetish powder. Used especially to secure the constitutional effect of mercury in infantile syphilis. Dose, 0.25 Gm., 4 grains, equivalent to about 0.1 Gm. of metallic mercury, in powders or capsules. *Mercury Mass* (Blue Mass, Blue Pill) contains 33 per cent Hg. Dose, 0.2 Gm., 3 grains; used similarly to calomel. ***Strong Mercurial Ointment,** U.S.P. (Unguentum Hydrargyri Forte), contains 50 per cent Hg, emulsified by 8 per cent of mercury oleate, in wool fat, white wax and petrolatum. Used for inunction. *Mild Mercurial Ointment,* U.S.P. (Ung. Hydrargyri Mite; Blue Ointment, Diluted Mercurial Ointment), contains 10 per cent Hg (formerly 30 per cent!). Used against cutaneous parasites.

INSOLUBLE MERCUROUS COMPOUNDS.—***Mild Mercurous Chloride,** U.S.P. (Hydrargyri Chloridum Mite; Calomel, Protochloride of Mercury); HgCl; a fine white powder, odorless and tasteless. Practically insol. in water or alc. Incompatible with alkalis; oxidizing acids; iodides and bromides; and with a mixture of sod. bicarb. and antipyrine (J.A.M.A., *56:* 287, 1911). Dose, laxative, 0.12 Gm. (0.03 to 0.2 Gm.), 2 grains (½ to 3 grains), as powder or tablets; intramuscularly, 30 to 60 mg. *Yellow Mercurous Iodide,* N.F. (Hydrarg. Iodidum Flavum; Protoiodide of Mercury); a bright, yellow, odorless, tasteless, amorphus powder; almost insol. in water. On exposure to light, it darkens by decomposition into mercuric iodide and metallic mercury. Incompatible with oxidizing agents, alkalis and carbonates, chlorides, bromides and iodides. Dose, 10 mg., ⅙ grain (maximum, 1 grain). "*Green Iodide*" is an analogous salt prepared by a different method. It is said to be less potent.

INSOLUBLE MERCURIC COMPOUNDS.—***Mercuric Salicylate, U.S.P. (Hydrargyri Salicylas); containing about 57 per cent Hg; a white, slightly yellowish or slightly pinkish powder. Nearly insol. in water; sol. in alkalis,** forming a double salt. Dose, intramuscularly, 60 mg. as suspension in oil, twice a week. *Mercuric Salicylate Injection*, U.S.P., a suspension in fixed oil, usually available as 0.06 Gm., 0.1 Gm., and 0.12 Gm. in one cc. *Ammoniated Mercury*, U.S.P. (Hydrargyrum Ammoniatum; White Precipitate); NH_2HgCl; a white, amorphous, insol. powder, obtained by precipitating $HgCl_2$ by ammonia. Represents about 79 per cent Hg. Irritating and not used internally. Employed externally against eczema and parasitic skin disease, especially pediculi, as dusting powder, but chiefly as *Ammoniated Mercury Ointment*, U.S.P., 5 per cent (formerly 10 per cent). Its absorption from the ointment is reported by O. S. Gibbs, Shank and Pond, 1941. *Yellow Mercuric Oxide*, U.S.P. (Hydrarg. Oxidum Flavum; Yellow Precipitate); a light orange-yellow amorphous powder, turns darker on exposure to light. Odorless; somewhat metallic taste. Nearly insol. in water or alc. Incompatible with acids. Maximum dose, 0.03 Gm., $\frac{1}{2}$ grain. Applied chiefly as *Ointment of Yellow Mercuric Oxide*, U.S.P., 1 per cent. It is used in ophthalmology against inflammations of the lids and conjunctiva, diluted with petrolatum so as to contain $\frac{1}{12}$ to 1 per cent of the oxide. "Pagenstecher's Ointment" contains 4 per cent. *Oleate of Mercury*, U.S.P. (Oleatum Hydrargyri), is made by dissolving 25 per cent of yellow mercuric oxide in oleic acid.

SOLUBLE MERCURIC SALTS.—***Mercuric Bichloride**, U.S.P. (Hydrargyri Bichloridum; Corrosive Sublimate, Bichloride or Perchloride of Mercury); $HgCl_2$; occurs as heavy, colorless crystals or white powder of acrid metallic taste. Slowly sol. in water (1:13.5), freely sol. in alc. (1:3.8), sol. in glyc. (1:12) or eth. (1:22). Its solubility in water is increased by ammonium or sodium chloride and tartaric or citric acid ("Sal Alembroth" = 2 parts of $HgCl_2$, 1 part NaCl). Incompatible with alkalis and carbonates; iodides; many alkaloids and other organic compounds and reducing agents. Dose, 2 to 4 mg., $\frac{1}{32}$ to $\frac{1}{16}$ grain. The discovery of mercuric chloride is attributed to the Arabian alchemist Geber, of the seventh century. Rhazes and others employed it against skin eruptions ("leprosy"). ***Large Poison Tablets of Mercury Bichloride**, U.S.P. (Toxitabellae Hydrargyri Bichloridi; Corrosive Sublimate Tablets, Bichloride Tablets). In order to guard against accidents, the U.S.P. directs these tablets to be of a distinctive color and of an angular, not disk shape. Each tablet contains about 0.47 Gm. of $HgCl_2$, and about 0.5 Gm. of NaCl. These tablets should be dispensed in securely stoppered glass containers on the exterior of which is placed a red label bearing the word "Poison" and a statement of the amount of corrosive chloride in each tablet. One tablet to 1 pint of water makes an approximately 1:1000 solution.—*Small Poison Tablets of Mercuric Chloride*, U.S.P., are similar, but contain about 0.125 Gm. of $HgCl_2$. One tablet to 4 ounces of water furnishes an approximately 1:1000 solution. *Red Mercuric Iodide* (Hydrarg. Oxidum Rubrum; Biniodide); HgI_2; is a scarlet red, odorless and tasteless powder. Nearly insol. in water; rendered soluble by the presence of four-fifths its weight of KI and NaI. Incompatible with alkalis and carbonates and alkaloids. Dose, 2 to 4 mg., $\frac{1}{32}$ to $\frac{1}{16}$ grain; maximum, 20 mg., $\frac{1}{3}$ grain. *Potassium Mercuric Iodide*, N.N.R., K_2HgI_4, is usually made as extemporaneous solution, by dissolving HgI_2 or $HgCl_2$ in excess of KI (1:4). For intramuscular injection, the corresponding sodium salt is preferred (HgI_2 = 1; NaI = 3; Water = 100). Dose, 0.4 cc. = 4 mg., $\frac{1}{16}$ grain. *Mercuric succinimide*, U.S.P., about 50 per cent Hg, soluble in water (1:20). Average dose, 15 mg., intramuscularly.

LEAD

The lead salts precipitate proteins and therefore act as local astringents. Their acute toxicity is low, as they are absorbed rather slowly; but they tend to produce cumulative effects. Chronic lead poisoning is a common disease with characteristic symptoms: the "lead line" at the margin of the gums; marasmus and anemia; paroxysmal colic and arthralgias; "wrist drop" and other peripheral motor paralyses; central motor stimulations (tremors and convulsions); psychic changes (encephalopathia), and so forth. The mechanisms and relations of these effects are not definitely known. On withdrawal from the lead, the phenomena generally recede more or less completely; but the patient may remain in bad health and over-susceptible to lead, for some time. Prophylaxis against lead poisoning is more important than treatment.

The root growth of *plants* is retarded by dilutions of 1:100,000 in the nutrient solution (Hammet, 1929), probably by combining with *sulfhydryl groups* and so interfering with enzyme processes. Very small amounts decrease the oxygen consumption of *excised tissues*. Concentrations higher than 1:20,000 inhibit the germination of *frog spawn* (Dilling, 1926) and of *chick embryos*.

Astringent Actions.—Lead acetate and subacetate ("lead water") produce more astringent and less irritant effects than other soluble metallic salts. They are effective against diarrhea and catarrhal inflammations; but they are so liable to produce chronic poisoning that they should never be used internally or on open surfaces. Their use should be avoided even on the skin and in any case should not be long continued.

Lead subacetate solution should not be used on the eye, for in the presence of corneal ulcers it leads to persistent white incrustations which interfere with vision (Fantus). "*Lead and opium wash*" was used on superficial contusions. Saturated alcoholic solution of lead acetate was employed in Rhus ("Ivy") poisoning. Emplastrum Plumbi, "*Diachylon plaster*," acts as a mild irritant.

Acute lead poisoning is uncommon. It is generally produced by the acetate or subacetate, sometimes by the carbonate (white lead). The phenomena are at first local and not immediately dangerous, but they are often followed by chronic poisoning. Application to the skin (lead wash, Diachylon plaster) has rarely if ever caused acute poisoning (Paessler, 1804). Diachylon pills (as abortifacient) have proved toxic (A. Hall and Ransom, 1906; W. F. Warner, 1907).

The *acute symptoms* start with the taste, which for the soluble salts is at first sweet, then disagreeably metallic and astringent, with dry throat. This is followed in fifteen or thirty minutes (rarely after several hours) by thirst; burning abdominal pain (not to be confused with "lead colic") and vomiting, which often appears milky from lead chloride; this is followed by diarrhea, more rarely by constipation. The stools are black from lead sulfide. The urine is often scanty, with albumin and casts. Colic may occur in two or three days, especially if the administration is continued. It is generally accompanied by constipation; rarely by diarrhea. The patients are debilitated. There may be muscle cramps. Severe cases of acute lead poisoning develop collapse with slow pulse and finally coma, which is probably uremic. Convulsions may or may not appear. Death occurs usually within thirty-six hours. Most patients *recover* in two or three days from the acute effects, but the convalescence is slow; after a few weeks they show the phenomena of chronic poisoning (also animals, Dauwe, 1907).

Pathology of Acute Lead Poisoning.—The local effects are quite superficial. The gastric mucosa is somewhat blanched (astringent action), sometimes with ecchymoses or slight erosions. These changes may extend into the intestines; but the lower intestines are tinted black by the lead sulfide.

Of *soluble lead salts*, 10 Gm. are said to have produced death; and 30 Gm. may be survived (Kunkel). Fifty Gm. of lead acetate are probably always fatal. Formerly, lead acetate was used therapeutically in doses of 1 to 4 Gm.; but 2 to 3 Gm. have produced toxic effects. Of *lead carbonate*, 40 to 50 Gm. are said to have caused death (Brouardel). Of *lead chromate* a few centigrams are fatal, but this is attributed to the chromic acid (Brouardel). The toxicity of various lead pigments is reviewed by A. Hamilton, 1913.

Treatment of Acute Poisoning by Soluble Lead Salts.—The stomach must be emptied, preferably by lavage. This may be preceded by the administration of a soluble sulfate (sodium or magnesium). Animals are thus saved from several times the fatal dose (Dauwe, 1907); 1 per cent sodium sulfate may be used in the lavage. Milk, eggs or tannin are useful. A cathartic should be given after the stomach has been emptied. Subacute colic is treated as in chronic plumbism. Iodide is commonly given in the after-treatment.

Subacute lead poisoning is produced by repeated administration of acutely toxic or slightly subtoxic doses, with criminal intent, or in food contaminations, or therapeutically.

With large doses, each administration is followed by the gastro-intestinal symptoms of acute poisoning; dyspepsia and anorexia in the intervals. With subtoxic doses, the gastro-intestinal symptoms develop more slowly. Typical phenomina of chronic poisoning may start in a few days, with the lead line, headache, cramps, paralysis, especially of the upper extremities, nephritis and uremic coma and convulsions, ending in death (Brouardel, 1914).

Intravenous injections of soluble lead salts produce enteritis (through paralysis of capillaries). This does not involve the stomach (Orfila). If death is delayed, nephritis develops. Thouvenet also described liver changes (Brouardel). The intravenous toxicity of various compounds is reported by F. Bischoff *et al.*, 1928.

Lead Injections in Cancer.—W. Blair Bell, 1922, claimed that the intravenous injection of colloidal lead is beneficial in clinical cancer, both directly and by increasing the efficiency of x-ray treatment. Others have reported variable results. Sometimes there is apparent temporary improvement, which has been attributed to necrosis of the tumor in consequence of blocking of its capillaries by lead particles. Arrigoni, 1930, found necrobiotic changes in the blastomatous tissue, but also toxic actions on normal parenchyma, especially in the liver and kidneys. The injection may cause serious plumbism and appears scarcely advisable. The *fate of colloidal lead* was studied by Dilling and Haworth, 1929, in cats and rabbits.

Acute Toxicity.—Colloidal lead as such has no immediate effects; but it passes readily into salts, and the intravenous injection of such solutions causes marked fall of blood pressure and heart block. The solution should therefore be tested for this action (Dilling, 1929).

Mouse and *rat tumors* have been treated with lead and a variety of organic lead compounds, including tetraethyl lead. McMarsh and Simpson, 1927, and H. E. Eggers, 1934, obtained negative results; Datnow, 1935, tested twenty-seven organic lead compounds on the Brown-Pearce strain in rabbits and considered the results rather promising.

Absorption of Lead.—All lead compounds (with the possible exception of the silicate) are absorbable from all mucous membranes and exposed tissues. Absorption from the intact skin has not been definitely proved, but could probably occur to a limited extent through the cutaneous glands and hair follicles. The digestive and respiratory tracts are the principal avenues of entrance; their relative importance is difficult to judge, since inhaled lead fumes or dust or paint spray are largely swallowed. There is no doubt, however, that abundant absorption occurs directly from the nasopharynx and from the respiratory tract (Blumgart, 1923). Lead on the hands generally reaches the mouth with food, and is therefore absorbed from the digestive tract. The lead must be in solution before it is absorbed; but even the most "insoluble" lead salts and metallic lead if finely divided are somewhat soluble in the digestive juices and tissues; the "soluble" salts are to a considerable extent precipitated. The greater part of the ingested lead, soluble as well as "insoluble," is not absorbed. A quantity harmless as a single dose may be toxic when divided into smaller doses and thus spread over some days (review, A. S. Minot, 1938).

The *solubility of lead compounds in the digestive tract and tissues* is independent of their solubility in water. In the stomach, lead carbonate and even lead sulfate are dissolved fairly readily, being converted into chloride, by the aid of gastric juice. The solubility corresponds to that in HCl of corresponding strength. Peptone (0.2 to 1 per cent) facilitates the solution of lead salts; bile does not. Alkalis, including milk, diminish the solution (Carlson and Woelfel, 1913). Alkalis of the concentration of the pancreatic and intestinal juices convert lead sulfate into carbonate and lead carbonate into a mixture of neutral and basic carbonate (Auerbach and Pick, 1913). In the large intestine a part of the unabsorbed lead is converted into sulfide, as indicated by the black color of the stools; but this is prevented or diminished, as the sulfide may be redissolved, if an acid reaction prevails. Lead is also rendered soluble on the bronchial mucosa, presumably as protein combinations. The *sulfide* was supposed to be inabsorbable, but Woelfel and Carlson, 1914, showed that it is absorbed sufficiently, even from ores, to be dangerous. Lead *silicate* appears to be unabsorbable (Shie, 1921). The solubility of lead salts in balanced physiologic saline solutions was investigated by L. C. Maxwell and Bischoff, 1929.

The sulfate is less toxic than the more soluble carbonate; but both produce poisoning in adequate doses; for instance, 0.1 Gm. per Kg. per day (Carlson and Woelfel, 1913). The toxicity of a variety of inorganic and organic lead compounds is reported by J. S. Buck and Kumro, 1930; that of various lead pigments is reviewed by A. Hamilton, 1912.

Absorption from Respiratory Tract.—Lead may enter the respiratory passages as dust, in white lead works; as spray, in painting; and as fumes from heated lead. Molten lead volatilizes below its ebullition temperature (Shie, 1921). The fumes are converted into oxides (Teleky). The greater part of inhaled lead is caught in the nasopharynx and swallowed (Carlson and Woelfel, 1913). Lead poisoning often develops more rapidly with inhalation than with other methods (Aub, 1935), because inhaled lead is likely to be more finely divided (Teleky). However, it has been shown by ligation experiments that lead compounds are readily absorbed directly from the lungs (Tanquerel des Planches, 1839; Minot, 1924) and from the nasopharynx (Blumgart, 1923).

Absorption from Conjunctiva.—Poisoning has been produced by the long-continued use of a lead eye wash.

Absorption from Skin.—The application of lead washes or ointments to the skin may lead to poisoning; but the positive results may be referred to transfer of the lead to the mouth, or to injuries of the skin, so that absorption from the intact skin has not been established. The coloring of hair by lead indicates, however, that this may penetrate at least into these structures, and therefore presumably also into the epidermis; metallic lead and finely powdered compounds could perhaps be rubbed into the hair follicles and then be dissolved and absorbed analogous to mercury and calomel inunctions; but the amount of this absorption appears to be negligible (P. O. Sussmann, 1922). Some absorption occurs from diachylon plaster (R. Schmid, 1942). Canuet and Drouet found that dogs or rabbits may be poisoned by baths of lead acetate, but Potain showed that poisoning does not occur if the animals are prevented from licking the skin (Brouardel); Beresina and Engling, 1887, found blood changes in guinea pigs after two days of inunction with 10 per cent lead carbonate ointment. The changes were greater when a lanolin base was used than with petrolatum base. *Absorption from denuded skin* may be an occasional source of poisoning in workers, whose skin is often thinned, macerated or chapped.

Absorption from Hypodermic Injections of Lead Carbonate.—Straub and Erlenmeyer, 1913, utilized this for the production of experimental plumbism. In cats, the lead was absorbed from the hypodermic deposits at the rate of 0.1 to 1 mg. per Kg. per day.

The excretion of lead occurs mainly by the feces and urine. The fecal lead is partly unabsorbed, partly excreted directly into the intestines, with small quantities by the bile and pancreas (Bricker, 1926). Insignificant traces of lead may occur in milk (Baum and Selig, 1895), saliva (Pouchet, 1880), sputum (Meillere, 1903) and sweat (after pilocarpine, Spillman). The excretion by the skin is negligible. The application of sulfur and sulfides to the skin of lead workers often gives a black color, which indicates exposure to lead, but this is due to adherent nonabsorbed lead, and not to excreted lead (Miura). Lead passes into the fetal circulation (Annino, 1893) and this may be a factor in the frequent abortions.

The *fecal excretion* is generally greater than the urinary, but the proportion varies. During the ingestion of lead, a large part of the fecal lead may be unabsorbed lead sulfide. After the patient has been withdrawn from exposure for some time, the ratio of fecal to urinary lead averages about 2.5:1 (Aub *et al.*). Normal feces contain about 0.08 mg. of lead per gram of ash (Kehoe and Thamann, 1929).

Time of Excretion in Urine.—After 0.02 Gm. of lead, taken by mouth, Riva, 1913, found demonstrable quantities in the urine only after three or four days. The excretion continued for a considerable time after the administration had ceased.

Compounds Excreted.—Unabsorbed lead occurs in the feces largely as sulfides; but absorbed lead is said to be excreted entirely as organic compounds (Erlenmeyer, 1913).

The *daily lead excretion* has been studied especially by Kehoe *et al.*, 1928, 1935, 1940. Under average conditions of American life the total excretion amounts to about 0.25 mg. (0.2 to 0.4) per day, of which 0.24 mg. is in the feces. This is practically equal to the ordinary food intake of lead, 0.32 mg. (0.1 to 2 mg.) in various regions of the United States, so that income and output are in equilibrium and there is little if any retention and accumulation. Under more primitive conditions, as in rural Mexico, the excretion is about half of this amount (0.12 mg.). In patients with lead poisoning it amounts to 0.3 to 1 mg. or more; in patients recovering from chronic plumbism, Aub *et al.* found an average of 0.4 mg.

The *urinary concentration*, per liter, averaged 0.014 mg. under primitive conditions; 0.04 mg. under ordinary conditions; 0.1 to 0.2 in lead poisoning, to 1 mg. in severe cases. The daily urinary output is normally between 0.02 and 0.08 mg.; in the convalescent group it ranged from 0 to 0.32 mg.

Diagnostic Significance.—The demonstration of more than 0.05 mg. of lead per liter of urine, or 0.15 mg. per day, indicates that abnormal amounts are circulating in the blood and are a warning, although concentrations of 0.05 to 0.15 mg. per 100 cc. of urine, or 0.06 to 0.07 for blood, may exist for months without deleterious effects (Kehoe *et al.*, 1940). Fecal lead beyond 0.6 mg. daily also indicates excessive exposure. The concentration is not necessarily proportional to the severity of the symptoms, for these depend largely upon the cumulative injury; moreover, the concentration may vary from day to day by the mobilization of the lead deposited in the bones; and finally, the lead nephritis may interfere with the urinary excretion, so that it may fail to reveal lead, although the blood contains 0.05 to 0.1 mg. per 100 cc. Diuresis does not materially affect the daily urinary output (S. H. Webster, 1941).

Retention of Lead.—If the income of absorbable lead exceeds the normal, the elimination also increases so as almost to balance the intake, but a part is retained and laid down in insoluble form, to a slight extent in the soft tissues as with other metals, but chiefly in the trabecular bone, analogous to calcium. The total amount so retained is not large; Aub estimates that an adult dying of chronic lead poisoning would probably not contain more than 1 gram altogether, and most of this would be in the skeleton. As the bone is reabsorbed, the lead is remobilized, and partly excreted, partly redeposited. The excretion is therefore slow, intermittent and prolonged, traces appearing in the urine and feces for months and even years after the absorption has stopped.

With *intravenous injection* of lead, the greater part is stored (Aub, 1935). *With oral ingestion*, the *amount* retained varies directly with the level of the intake and with the duration of this level; but the *percentage* retained is greater for low levels and short duration (Cowgill and Horwitt, 1938; Calvery *et al.*, 1938). The storage varies inversely as the *calcium of the diet* (Calvery *et al.*, 1938), owing to the interference of calcium with the absorption of lead, presumably by forming a less soluble salt (Lederer and Bing, 1940). Retention of calcium is inverse to that of lead. Lead retention is also increased by low phosphate income; but calcium or phosphate does not protect rats against excessive lead income (J. B. Shields and Mitchell, 1941). Calcium storage is increased by the administration of vitamin D (Sobel *et al.*, 1939). Growing animals store relatively more than adults (Shields *et al.*, 1939). Addition of 0.2 per cent of *ferrous sulfate* to the diet of rats tends to prevent lead acetate anemia and stunting in rats, presumably by interfering with lead absorption (Heppel and Kornberg, 1946).

"*Normal Lead.*"—Small amounts of lead are present in normal individuals, not as a necessary element, but because exposure to lead is universal. The difference from that found in lead poisoning is merely quantitative (human, W. Cone *et al.*, 1934; animals, Dankworth and Höll, 1934; fowl, Ciurea, 1931).

The **distribution of lead in the organs** is approximately the same for various compounds, including tetraethyl lead, and for different methods of administration, but it undergoes a change with time: Early after the absorption, the greater part of the lead is in the kidneys and liver; after several days it shifts toward the bones, and in chronic poisoning these contain a third to nearly the whole of the lead (A. S. Minot, 1924). Next comes the liver, which accounts for 0 to 28 per cent of the lead; then the kidneys (0 to 14 per cent). Only small quantities are contained in the other parts. These figures are from experimental animals (H. P. Morris and Long, 1939; radioactive isotopes, Lomholt, 1930, Behrens, 1934); but the concentrations in human cases indicate that the phenomena are strictly analogous. Lead passes across the placental circulation into the *fetus;* the quantity in the newborn is proportional to the amount ingested by the mother (E. P. Lang, Morris *et al.*, 1937).

Human hair contains considerable lead, normally 0.5 to 4 mg., averaging 1.7 mg. per 100 Gm. In lead industries the content is 16 to 230 mg. after thorough washing (H. Kraut and Weber, 1944. These workers deny any relation to the color of the hair, which had been asserted by K. N. Bagchi *et al.*, 1940).

The *concentrations in the more important organs of human lead poisoning*, under a variety of conditions, ranged as follows, mg. per 100 Gm. of moist tissue (Aub): Teeth, 5 to 20; skeleton, 2.2 to 15 (total, 200 to 800 mg.); liver, 0.1 to 5; kidneys, 0.1 to 1; central nervous system, 0 to 0.36; muscle, 0; blood, trace to 0.27; cerebrospinal fluid, to 0.1.

In rats receiving lead compounds the concentration was in the sequence: Femur > kidney > brain > liver;

and with higher intake it changed to kidney > femur > liver > brain (H. P. Morris and Long, 1939). Chronic administration of radioactive isotope to rats and mice gave the sequence: Bone > liver > kidney (confined to cortex) > spleen > pancreas > intestines > heart > lung, brain (Lomholt, 1930; Behrens, 1934).

The *blood concentration* is of diagnostic significance: The normal average, mg. per 100 cc., is 0.03 (Kaplan and McDonald, 1938); 0.06 (Kehoe *et al.*); 0.054 (Thompsett and Chalmers, 1939). Concentrations above 0.06 suggest lead poisoning. J. N. Chalmers, 1940, found 0.03 to 0.09 in seventy normal people in England; and 0.06 to 0.19 in forty-four lead workers without symptoms. Kaplan and McDonald found 0.1 to 0.6 in early clinical lead poisoning; and 0.4 to 0.6 in fatal encephalitis.

Distribution between Cells and Plasma.—The average lead concentration of the blood is ten to fifteen times higher than the average concentration of the urine, but about 90 per cent is contained in the cells, in clinical lead poisoning and in normal individuals (K. Bambach *et al.*, 1942). The plasma level is not far different from the urine concentration. F. L. Smith *et al.*, 1938, found the lead concentration of normal persons to range from 0 to 0.01 mg. per 100 Gm. for serum and 0.02 to 0.11 mg. for the cells. After intravenous injection of radioactive lead, up to 99 per cent of the lead in the blood is in the cells, within a few minutes (K. A. Mortensen and Kellogg, 1944).

BAL Mobilization of Erythrocyte Lead.—A single intramuscular injection of 5 mg. per Kg. of body weight into workers exposed to lead results in a prompt decrease of the lead concentration of the blood cells, demonstrable within a few minutes, maximal in eight hours, and returning to the previous level in twenty-four to forty-eight hours. This effect is much greater than is producible by any other agency. The cycle is repeated with further injections. The lead concentration of the plasma is not materially changed so that the released lead must leave the plasma rapidly, presumably into the tissues and urine. The urinary lead is distinctly increased, reaching a peak in one to two hours and returning to the previous level in eight to twenty-four hours. The extra amount of lead eliminated by a single injection is too small to have therapeutic significance, and sufficiently repeated injections are precluded by the toxicity of the BAL (H. W. Ryder, Cholak and Kehoe, 1947).

Form of Lead in Blood.—The lead of the erythrocytes is not diminished by washing with isotonic saline (H. Blumberg and Scott, 1936). The quantity in the plasma is so small that its combination has not been identified with certainty. It was generally assumed to exist as albuminate, but according to elecrometric measurements and other considerations, it exists most probably as tri-lead phosphate, $Pb_3(PO_4)_2$, which is formed when any lead salt meets with sodium phosphate. This is soluble in water only to the extent of 0.13 mg. per liter, and therefore probably in part in colloidal solution (Aub). In acid reaction, the tri-lead phosphate is changed into bi-lead phosphate, $PbHPO_4$. This is nearly a hundred times more soluble in water than is the tri-lead phosphate, and therefore exists presumably in true solution and ionized. It could not exist at the *p*H of the blood; but Aub believes that it could be formed by local acidosis, and that this transformation is connected with the lead actions, as well as with the mobilization of lead from the bones, the latter along with the similar mobilization of the calcium salts. Other theories of lead combination have been proposed. L. C. Maxwell and Bischoff, 1929, suggested that it is carried as a diphosphoglycerate; Jowett, 1932, believed that it forms a complex inorganic phosphate with calcium and chloride. If lead ions are added to blood serum in concentrations not over 1:10,000, they disappear from the solution almost immediately by adsorption on the protein colloids (Teisinger, 1935). Serum dissolves 12.5 to 33 mg. of lead carbonate per liter, *in vitro. Cerebrospinal fluid* contains lead in about the same concentration as blood (Aub *et al.*, 1926; Rabinowitch *et al.*, 1933; A. J. Hyman, 1934).

Lead deposition in bone and teeth is closely parallel to that of calcium, as was recognized by A. Gusserow, 1861. Lead is in no way necessary to bone formation, but accumulates passively as the insoluble tri-lead phosphate, apparently by its similarity to the calcium phosphate of the bone, perhaps incorporated into the apatite pattern. It is therefore deposited when and where calcium is laid down in the bone, in the trabeculae and in the actively growing epiphysis; and remobilized when and as calcium is mobilized (Aub *et al.*, 1932). The amount deposited varies directly with the income (Calvery *et al.*, 1938) and therefore increases with age; but the rate of deposition for a given income level is greater in the young than in the mature (Calvery *et al.*, 1938; Kasahara and Nosu, 1934). The age difference is greater in compact than in spongy bone (H. P. Morris, 1940). The total amount deposited is not large, even in pronounced clinical lead poisoning, scarcely ever above 150 mg. per Kg. of fresh bone, or 0.2 to 0.8 Gm. in the entire skeleton (Aub, 1935). Bones of normal individuals without special exposure contain 0.5 to 10 mg. per 100 Gm. of ash; the higher concentration in older people, the lowest in infants. The lead of soft tissues does not increase with age (review, A. S. Minot, 1938). Lead in old age amounts only to 0.003 per cent of the bone ash, and a fifth of this in infancy (Barth, 1931).

The *distribution of lead* in the bones can be followed grossly and microscopically by decalcifying with formic acid and exposing to hydrogen sulfide. The deposition occurs on all surfaces exposed to the blood, in the periosteal and endosteal layers, in the Haversian and Volkmann canals, in the lacunae and bone canals, in the outer layers of the trabeculae and in the ossifying areas of the epiphyseal zones (E. Sieber, 1936), but not in the cartilage (Kasahara and Nosu, 1934). It is first laid down as dispersed colloid, then as crystalline masses (L. T. Fairhall, 1943). The lead content of the trabeculae averaged 80 per cent higher than that of the solid bone (Aub *et al.*, 1932); the ends of the femur 60 per cent more than the shaft (Calvery *et al.*, 1936). In children with serious lead poisoning, the epiphyses and kidneys were richest in lead (A. J. Hyman, 1934). Radioactive lead isotope (thorium 13) administered to mice and rats was more abundant in the subepiphyseal portion of long bones and subperiosteum of the ribs. Marked lead deposition occurred in young callus; rickets diminished the deposition of the lead, as did also overdosage of vitamin D. Lead was also deposited in pathologic calcifications (Behrens and Baumann, 1933). The concentration of lead *in fresh whole bone* of human adults not especially exposed to lead was stated by A. S. Minot and Aub, 1924, as not more than 2 mg. per 100 Gm. Tompsett, 1936, found in nineteen autopsies, 0.34 to 1.75 mg. in the ribs and vertebrae, 1.5 to 10.8 mg. in the femurs and tibias. In the *teeth*, the lead is chiefly in dentine, traces in the enamel (Pfrieme, 1934). The *bone formation* itself is altered when growing children are exposed to chronic lead poisoning, the roentgen shadows being similar to those produced by overdosage of viosterol, with transverse lines of greater density behind the diaphyses. Similar changes were produced in growing dogs, but not in full grown dogs (J. Caffey, 1931; Kasahara and Hiroshima, 1934). The bones are softer and more fragile than normal (Calvery *et al.*, 1938). The blood calcium decreases in the early stages and rises later in chronic lead poisoning (Pavloff, 1927).

Mobilization of lead from the bone occurs in man and in animals by the same agencies that mobilize calcium, notably acidosis as result of disease or the administration of the drugs that acidify the urine, such as ammonium chloride; lead is also mobilized by administration of sodium bicarbonate, probably because the carbonate is more soluble than the phosphate; and by potassium iodide. The iodide effect is as large as that of the acidosis, but its mechanism is obscure. All these increase the fecal excretion of lead to two or three times; the urinary excretion is not much altered. The effect of magnesium sulfate is doubtful (Aub *et al.*, 1932). Rise of the blood level of lead can be demonstrated (Teisinger, 1938). Low-calcium diet also mobilizes lead and raises its concentration in the blood, while this is lowered by high-calcium diet (Tompsett and Chalmers, 1939). Acidifying doses of calcium chloride produce mobilization (F. Schmitt and Basse, 1937). Parathyroid administration mobilizes lead in animals, but not clinically (Teisinger). Vitamin D in moderate doses promotes the storage of lead. Administration of neutral ammonium phosphate, lactic acid, sodium citrate or potassium chloride had no effect (Aub).

The following doses produce the mobilization clinically: ammonium chloride, 1 Gm. in a glass of water, ten to twelve times per day; dilute phosphoric acid (10 per cent), 20 cc. in a glass of sweetened water every hour, about ten times daily; sodium bicarbonate, 20 to 40 Gm. per day; potassium iodide, 0.5 to 2.5 Gm. per day.

Accidental or incidental mobilization of lead is credited with the periodic acute exacerbations of symptoms in chronic plumbism, especially in the acidosis of pneumonia, surgical operations and alcoholism. Iodide or bicarbonate is sometimes used to provoke lead excretion for diagnosis, but may bring on an acute symptomatic attack. Carefully managed mobilization is used for the removal of stored lead in the quiescent intervals (Aub).

Chronic Lead Poisoning (Plumbism; Saturnism).—Daily absorption of small quantities of lead occurs in numerous industries that employ lead or its compounds, and sometimes also from contaminated water or food. Chronic lead poisoning (plumbism, saturnism) is therefore common. It is especially dangerous because it develops insidiously, and is often not recognized until it is far advanced.

The symptoms involve the nutrition, the blood, and nervous and muscular structures, apparently independently. Eventually there may be degeneration of the kidneys and other organs. The effects are arrested if the patient is withdrawn from exposure to lead, usually with fairly prompt and apparently complete recovery, aside from anatomic lesions.

Animals are also subject to chronic lead poisoning, and show practically the same symptoms. Some of the phenomena may be produced acutely by the injection of organic compounds; but it is questionable whether these are identical with those of chronic poisoning.

Sources of chronic lead poisoning are found in many industries, especially through the use of paint; in food or drink contaminated by lead-containing vessels or pipes, by insecticides, and by other accidental sources; by cosmetics and sometimes medicines; by leaden bullets, and so on. Artisans working with paints are the most common victims. The manufacture of storage batteries is also an important source of poisoning. However, the metal is so widely distributed that everyone is to some extent exposed. The hazards of tetraethyl lead will be considered in a special section.

Industrial Lead Poisoning.—In 1921, Shie reported that about 200 American industries use lead, and the number is constantly increasing. Prophylaxis has become increasingly effective, however, so that lead fatalities decreased from 2.5 per million in 1910, to 1.1 in 1928 (F. L. Hoffman, 1930). The hazard at present is greatest in smaller establishments where adequate precautions are not enforced (review, L. T. Fairhall, 1945; "Occupational Lead Exposure," Am. Pub. Health Assoc., N.Y., 1943).

The more important lead trades are: Production.—Roasters of lead ore; manufacture of lead pigments and paints (white and red lead; lead chromate). The smoke and fumes of lead smelters may contain considerable lead which is harmful, not only by direct inhalation, but also by being deposited on vegetables cultivated in the vicinity. Animals grazing in such localities are often affected. The determination of lead in metallic fumes is discussed by R. G. Keenan and Fairhall, 1944. *Pigments.*—Painters, enamelers; varnishers; automobile work; glazers; dyers; paper; silk; artificial flowers; rubber goods; potters. Among *painters*, about 40 per cent show active symptoms. Less than half of those who have passed the age of forty years are free from plumbism. The heaviest incidence is among those who have been painters for ten years or longer (Harris, 1918). The spraying method of painting presents special dangers (Hamilton). Poisoning has been caused by the smoke from burning painted wood. *Children* may be severely poisoned by gnawing the lead paint of their toys or beds (Blackfan, 1917). *Metal.*—Plumbers; printers (handling type); file cutters; glass and gem cutters; storage batteries.

Lead in Food and Drink: Leaden water pipes and lead, tin and pewter vessels were prolific sources of danger, which have been largely but not completely eliminated. The use of lead paint for tightening pipe joints presents some danger (H. B. Williams, 1939).

Water pipes are especially treacherous because the solubility of lead varies greatly with circumstances. If perfectly pure water is allowed to flow through bright and clean lead pipes, poisoning results invariably. The surface of the lead is changed into a hydrate (Clowes, 1902), and this is sufficiently soluble to cause the intoxication. The danger is much less with old lead pipes; these become lined with a layer of lead oxide, PbO + Pb. This is quite insoluble, and does not readily form a hydrate. The solubility is increased by oxygen and salts, especially by nitrates (Fortner, 1905), but even by sulfates; it is diminished by carbonic acid and carbonates (Paul, etc., 1906). Hard water is therefore much less dangerous than soft water. (Details and older literature in Wolffhuegel, 1887.) Old lead pipes with hard water present relatively little danger; but should the water stand in the pipes for a time, some solution will occur. The use of lead pipes should therefore be avoided.

The actual lead content of water delivered from lead pipes has been found as 0.5 to 12 mg. of Pb per liter (Kunkel). In the Leipzig epidemic of 1930 it was 5.3 mg. per liter in the morning and 3.5 mg. per liter during the day. In two lead epidemics it was 14 mg. per liter (Brouardel). Angus Smith considered 0.35 mg. per liter as dangerous. From data to be quoted later, there is reason to believe that even 0.05 mg. is not indifferent. The U. S. Treasury Department sets 0.1 mg. per liter as the limit of lead in drinking waters. Fish have a high resistance to lead in water and thrive in a saturated solution of lead carbonate.

Lead, Tin and Pewter Vessels.—Leaden cooking utensils and containers for food or drink should be entirely discarded. Tin plate (cans), solder, pewter and tin foil usually also contain some lead. If the percentage does not exceed a certain limit (1 per cent for tin plate; 10 per cent for solder), the lead is held so firmly in the alloy that it is dissolved by moderately acid fluids, such as vinegar. These are deemed harmless. Evaporated milk bought from open shelf stock contained only the lead of the milk, allowing for the concentration (Fairhall, 1937). Higher proportions give up their lead and are dangerous. Some enamel ware contains soluble lead; but this is now believed to be exceptional. Earthenware and porcelain are glazed with lead silicate, and this is contained in varieties of glass; but if the lead is present only as silicate, it is harmless.

Millstones repaired with lead have contaminated *flour and bread.* The use of lead shot for cleaning bottles is dangerous. Clarification of wine with lead acetate is also dangerous.

The lead content of meat and fish was reported by O. Jones, 1946.

Spraying of fruit and vegetables with lead arsenate as insecticide is now extensively practiced and may leave considerable residue on the surface. The lead is generally the more toxic component. U.S. government regulations set a limit of 2.56 mg. of lead per Kg. of food, 0.018 grains per pound, which would correspond to 3.55 mg. for 3 pounds of daily food (the limit was formerly 2 mg. per Kg., 0.014 grains per pound). This limit is quite feasible if proper precautions are taken and fruit is washed in dilute acid.

The limitation was needed, as severe acute arsenical poisoning resulted from eating three apples from a sprayed orchard (Heeren and Funk, 1917), and even death has been reported (Hayhurst, 1920). The present limit appears to be safe, considering that sprayed food constitutes only a fraction of the diet. However, if even a third of the food contained the permitted maximum, this would amount to 1.025 mg. of lead, which would presumably become dangerous (Calvery, 1938). Further data are needed as to smaller amounts, in view of the cumulative nature of lead poisoning. The fear has also been expressed that continuous spraying may poison the soil itself.

The spraying of orchards with lead arsenate was introduced in 1894. Five or more sprays are applied in the season. Forty-four million pounds are used annually in the United States. An epidemiological field study of over 500 workers in sprayed apple orchards revealed only six cases with definite laboratory and clinical findings, but the latter were below "incipient plumbism." The urines almost always contained measurable amounts of arsenic and lead, even when there was no direct exposure. In exposed workers the urinary concentration of lead ranged from 0.068 to 0.123 mg. per liter; arsenic from 0.06 to 0.22 mg.; the blood concentration of lead from 0.039 to 0.052 mg. (P. A. Neal *et al.*, 1941). Fairhill and Neal, 1938, administered 10 mg. of lead arsenate, $PbHAsO_4$, per day to man for ten successive days without apparent untoward effects, but the period is too short for lead poisoning. Animal experiments indicate a greater degree of tolerance than it would be safe to transfer to man: Horwitt and Cowgill, 1937, raised three generations of normal rats on a diet containing 100 mg. of lead per Kg. of food, near forty times the official limit, and puppies also throve on 50 mg. per Kg., twenty times the official limit. Lead arsenate is sufficiently soluble in gastric juice to account for its absorption. When shaken with serum, dilead orthoarsenate forms soluble arsenates and insoluble pentalead chlorarsenate (Fairhall, 1939).

The *toxicity of lead azide* is discussed by Fairhall, Wendell *et al.*, 1943.

Cosmetics.—Lead carbonate, used as face powder or pomade, has caused plumbism. Kasahara and Hiroshima, 1934, reported bone changes characteristic of lead in 115 Japanese infants, caused for the most part by lead cosmetics on the skin of the mothers. Lead and sulfur hair dyes present at least a theoretical danger; although serious poisoning by them must be uncommon.

Medicines.—The internal use of lead is not advisable, although it may be harmless if it is temporary. Brief use of lead washes is safe, but prolonged application, especially to the denuded skin, is dangerous. This probably applies also to lead plaster. The plaster has been taken as abortifacient, with toxic results (Pope). The treatment of cancer by intravenous injection of colloidal lead has given rise to serious lead poisoning.

Lead Poisoning from Imbedded Bullets.—Projectiles left in the tissues do not readily give up their lead to the circulation, so that they may be harmless. Exceptionally, however, they produce severe and sometimes fatal plumbism, sometimes after a latent period of months or even years (Machle, 1940). Leschke, 1934, states that lead has been demonstrated in the blood ten years after the lead was imbedded, 0.01 mg. per 100 cc., increased to 0.175 mg. by bicarbonate treatment. The chances of intoxication are greater when the lead offers a large surface, as with small shot (Curtillet and Lombard, 1912). The possibility of eventual plumbism renders the removal of bullets advisable, even when they are not causing mechanical injury. However, in Curschmann's case an encephalitis saturnalis was precipitated by the manipulation of the scattered lead in the wound during the operative removal.

Swallowing of leaden bullets and shot usually produces plumbism, depending, however, on the time of sojourn in the digestive tract. Brouardel states that shot was formerly administered in volvulus, but that this was strongly condemned by Van Helmont and other masters of that period. He also describes some modern cases, in man, cows, dogs, and so on. *Birds* are especially subject to this form of plumbism, as the shot is picked up with food, and remains indefinitely in the gizzard or crop, where it is slowly ground and macerated. Six No. 6 shots are fatal to a duck (Wetmore, 1919). Hanzlik, 1921, found that ducks and pigeons die in two to three weeks, when 0.16 to 0.6 Gm. of lead per Kg. of bird has been absorbed. Other birds are similarly susceptible. When the total absorption averaged 0.01 Gm. per Kg. per day, the survival averaged eighty-three days. The symptoms consist in progressive anorexia and emaciation, starting in a few days, and proceeding to a loss of 40 per cent of the body weight at the time of death. The birds show visible crop peristalsis with regurgitation of fluid; diarrhea; paresis of extremities, with a "wing drop" simulating the "wrist drop" in man. The animals also develop dyspnea. Metallic lead is more toxic than its compounds when fed to birds (Hanzlik and Presho, 1923), doubtless because its softness permits it to be ground to a more colloidal powder, which can be more rapidly dissolved. *Other metals* are much less toxic to pigeons and do not produce the characteristic phenomena of the lead poisoning (Hanzlik and Presho, 1923).

The **susceptibility to lead poisoning** varies greatly, in the first place according to the precautions against exposure; but even when these are apparently the same, with men working side by side, some may be attacked in a few weeks, others may continue to work for forty years without notable symptoms (Shie). Wide variations in the time of onset and severity of symptoms occur even in animals selected and treated with a view to uniformity. Differences may depend on absorption and excretion, on the acid balance, the character of the food, digestive disturbances, starvation, anemia, infections, alcoholism and nephritis, and so on, and may therefore be important factors. Patients who have had an attack appear to be more susceptible to subsequent exposures; but this may only mean that the attack has revealed the susceptibility. Several observations, clinical (Legge and Goadby, 1912) and experimental (Weller, 1926), indicate that some individuals may acquire a degree of tolerance. Negroes are said to be more susceptible to encephalopathia.

The *quantity of lead required to produce chronic poisoning* can not be accurately stated, as it involves the time of exposure and other conditions, but it is generally considerably more than the average normal intake. There is some evidence that definite lead symptoms may result from the continued ingestion of 0.2 mg. per day, in addition to the normal dietary income which averages 0.25 to 0.35 mg. (H. B. Williams, 1939), but Kehoe *et al.*, 1940, found no deleterious effects on ingesting 1 mg. of lead, as acetate, daily for three and a half years, or 2 mg. one year.

The opinions of forty writers on the subject, compiled by Calvery, 1938, show that practically all consider 1.3

mg. per day as dangerous; 1 mg. is so considered by three-fourths, 0.65 mg. by half, and 0.325 mg. by a fourth. Epidemics of severe lead poisoning have been produced by water containing lead in quantities corresponding to the ingestion of 4 to 20 mg. per man, per day. This would be a maximal figure, and much smaller quantities are probably harmful. Brouardel believes that poisoning may result from 1 mg. per day; others place it much higher. W. Wright *et al.*, 1944, report that lead poisoning is common when the drinking water, over a period of years, supplies 1.5 mg. per day. Telekys, 1931, found that 1 to 2 mg. daily produced poisoning after some months, 10 mg. after some weeks. Gaertner claims that symptoms occur in man only after several months with a daily ingestion of 4 to 7 mg.; in three to four weeks, if the daily dose is 60 mg. (Fluegge and Heffter, 1912). In cats, 0.1 mg. per Kg. (corresponding to 6 mg. for man) may be absorbed daily for weeks without lead symptoms. Fatal lead poisoning requires the daily absorption of 1 mg. per Kg. or the daily ingestion of 12 to 30 mg. per Kg. Interference with appetite and growth may occur in rats with much smaller doses (Sollmann, 1921).

Time of Exposure.—The time required for the onset of noticeable symptoms varies greatly: in animals, from a day to several months; in man, from a few weeks to many years; in general, inversely to the dosage. The delay was formerly attributed to the gradual accumulation of effective concentrations of lead in the body; but as has been explained, the retained lead is practically entirely in inactive form in the bones. Straub, 1913, and Erlenmeyer, 1913, suggested that the cumulative action is due to the progressive accumulation of injuries, produced by the "stream" of circulating "active" lead, in course of absorption and excretion. The continuous mobilization of stored lead, with its periodic exacerbations, is doubtless an important factor in providing the active lead.

Characteristic Symptoms of Chronic Lead Poisoning.—These have a slow and vague beginning and run an irregular and intermittent course, with paroxysmal symptoms and recurrences. They may develop only some months after stopping work with lead. They are quite independent of the channel of introduction.

They begin generally with rather indefinite manifestations of ill health; digestive disturbances, especially anorexia and constipation; gingivitis and "lead line"; anemia, stippling of the corpuscles, disproportionate pallor; progressive loss of weight and of strength; rheumatic pains. Nephritis, gout, hypertension and arterioslcerosis, sterility, tuberculosis, and other chronic diseases are frequently associated with long-continued exposure to lead, probably mainly as secondary consequences.

A second group of phenomena occur as acute paroxysmal attacks of colic or sometimes arthralgias. A third group consists of motor paralyses, especially the "wrist drop." A fourth group are cerebral and bulbar phenomena, caused probably by hemorrhagic encephalitis, which are fortunately rare and confined to the most severe poisoning.

Frequency of Individual Symptoms.—Harris, 1918, found the named symptoms to occur in the following percentage of active cases among painters: Digestive disturbances are frequent. Loss of weight and of muscular strength are common complaints. Constipation, 72 per cent; backache (generally lumbar), 56 per cent; arthralgias, 56 per cent; anemia, 53 per cent; colic, 51 per cent; headache, severe frontal, 46 per cent; lead in urine, 46 per cent; hypertension (above 140 mm.), 39 per cent; pain in chest, 35 per cent; metallic taste, 18 per cent (this has no connection with the lead line); lead line, 14 per cent; stippling, 12 per cent; Wassermann test, negative, except in luetics.

Diagnostic Features.—The chief points may be recapitulated as: the history of exposure; lead line; ammonium sulfide reaction on the skin; black stools; especially the chemical demonstration of lead in the stools or urine; pallor, anemia, stippling, pinched features, asthenia, rheumatic pains, digestive symptoms, colic, obstipation, wrist drop, recovery when removed from exposure to lead. The concurrence of most of these signs is highly characteristic; but none of them is absolutely constant, and most may be simulated individually by other conditions (Linenthal, 1914).

Symptomatic Diagnosis.—With ordinary industrial poisoning, the *early symptoms* are not distinctive, but their absence tends to rule out lead poisoning. They consist chiefly of subjective complaints of poor health; exhaustion, ready fatigue, emotional irritability, anorexia, nausea, colic and constipation. Early objective phenomena are: skin pallor, blue line on gums, punctate basophilia, hematoporphyrinuria, flexor weakness. If any of these is present together with the subjective complaints, the patients should be removed from lead exposure. If they do not develop within a few weeks after starting the work, they will probably not develop at all; if they are absent after six months, the worker may be considered practically immune, provided that the conditions are not materially altered. Workers who have developed the minor manifestations, including the pallor, gum line and flexor weakness, may sometimes continue the exposure for years without developing more violent symptoms. Colic and epileptiform encephalopathy indicate recent and intense absorption of lead, generally superimposed on the more chronic symptoms, but occurring sometimes before these have had time to develop.

Experimental plumbism may be produced in mammals by *feeding* with lead compounds, especially the carbonate, either rapidly (Carlson and Woelfel, 1913) or slowly (rats, Weller, 1915; Sollmann, 1921); by scattering the carbonate on the sawdust of the cage (Wassermann, cats, 1916); in birds, by shot placed in the crop (Wetmore, 1918; Hanzlik, 1921); *hypodermically*, with lead carbonate (cats and guinea pigs, Straub, 1911 and 1914; Erlenmeyer, 1913). These methods require some weeks for the development of the typical symptoms. They resemble the human symptoms closely. *Dogs*, for instance, that received lead salts in their food, developed three grades of poisoning (Calvery *et al.*, 1938). *Mild:* apathy, loss of appetite, slight weakness of hind legs, loss of energy, early fatigue. *Intermediate:* paralysis of the hind legs, muscular incoordination, pain when handled. *Severe:* convulsions, severe pain, erethismus, tremors, impaired vision, muscular incoordination. The effects on *rats* were not so characteristic (E. P. Lang and Morris, 1938). Diets low in calcium increased the toxicity of the lead; the phosphate content had little effect (Calvery *et al.*, 1938). The phenomena in *birds* were described under the etiology. Somewhat similar symptoms may be produced acutely by the cautious *intravenous injection* of lead salts (Hirschfelder), but these acute effects probably have a quite different mechanism from the phenomena of chronic plumbism. Exposure of guinea pigs to the inhalation of lead oxide dust results in pneumonia (Ehrismann, 1939).

The *mechanism of the lead action* is obscure, but may conceivably involve several quite distinct factors. Some of the paroxysmal phenomena resemble flocculation reactions and could be connected with the unstable trilead and bilead phosphate system. Lead also alters the calcium level of the blood, decreasing it in the early stages, leading to increased sympathetic excitability, and lowering the calcium in the later stages with increase of parasympathetic excitability (Pavloff, 1927).

Details of Effects.—*Digestive disturbances* are among the earliest and most common phenomena. They begin with mild stomatitis, foul breath, sweet, metallic taste, anorexia and nausea. Diarrhea is frequent in the early stages; later there is usually obstinate constipation; or the two may alternate. The abdomen may be tender. These effects are based partly on mild inflammation of the whole alimentary tract, which later on is complicated by the colics. The anorexia is mainly responsible for the emaciation (sunken cheeks) and partly for the anemia, pallor, malaise, headache, insomnia, lethargy, weakness and tremors. Chronic parotitis sometimes occurs, perhaps as a part of the stomatitis. The lead line is a slate-colored margin of the gums where they meet the teeth. It is one of the earliest and most constant signs, and occurs also in animals. It shows that lead has circulated at some time, but not whether it is circulating at the moment. It is due to the precipitation of lead sulfide in the vascular subepithelial connective tissue. This is formed when the lead in the circulation comes in contact with hydrogen sulfide formed by putrefaction around unclean and carious teeth. The lead line therefore depends on the condition of the mouth, and may be prevented by oral hygiene. Its presence shows that the patient has absorbed notable quantities of lead, but it need have no relation to the lead symptoms. The buccal mucosa opposite carious teeth may also be blackened (Oliver's sign). A similar black line is given by bismuth, silver, mercury, iron and perhaps other metals. It may also be simulated by charcoal tooth powders. *Malnutrition, i. e.*, loss of weight, or checking of growth, is the earliest and most constant objective sign, and an almost quantitative index of lead poisoning.

In rats it is an inconstant feature, sometimes marked (Sollmann, 1921); sometimes slight (K. P. Morris and Laug, 1938); sometimes none, even with large doses (Horwitt and Cowgill, 1937). The difference has not been explained. In mice, Busch and Berman, 1927, found effects similar to those of thallium: Cessation of estrous cycle, alopecia, arrest of growth and occasionally cataract formation.

The *blood changes* in industrial plumbism begin early with polycythemia and polychromatophilia, rise of reticulocytes to double, and increase of the platelets. The red count and hemoglobin then return to normal, with further increase of reticulocytes. Basophilic granules, staining with methylene blue, appear in 500 to 1000 per million of the erythrocytes. This "stippling" is an important early diagnostic sign (van Emden and Kleerkoper, 1904), although the basophilic granules may occur in other anemias, and are sometimes absent in lead poisoning. With definite plumbism the proportion of basophilic cells increases, the total red count and the hemoglobin decrease below normal, poikilocytes and nucleated red cells appear, the percentage of large mononuclear cells increases, polymorphonuclears may be decreased, the platelets decrease (reviews, R. R. Jones, 1935; W. Machle, 1947).

In clinical cases the anemia is usually moderate, the count rarely falling below four millions. The color index is variable. Many corpuscles are destroyed, producing icterus and widely distributed "hemosiderin," and the appearance of hematoporphyrin in the urine. In animals, the erythrocytes often drop rapidly, from the first or second day, to about two-thirds of the normal, and remain at this level till death. If the lead is removed, the count rises rapidly. This severe anemia is probably due in part to inanition.

The *bone marrow changes* correspond to those produced by mercury, iron, phosphorus, and many infective and wasting diseases. They are perhaps secondary to anemia. At first there is marked increase of leukoblastic cells with disappearance of fat, and sometimes with moderate hyperemia; then, gelatinous degeneration and atrophy of the whole marrow tissue (R. Stockman and Charteris, 1903). The blood changes as a whole indicate increased destruction of the corpuscles, with consequent stimulation of the bone marrow to increased production of young cells. The resistance of the corpuscles to laking is increased, and this is somewhat diagnostic of lead poisoning. It is also seen when corpuscles are exposed to dilute lead solutions *in vitro;* it has been suggested that the lead hardens the surface, and so renders the cells less elastic and therefore more vulnerable to mechanical injury, and at the same time more resistant to chemicals (Aub). The *genesis of the basophilic granulations* is not clear. Their occurrence varies in individuals and especially in species. It has been suggested that they represent coagulation of the basophilic substance of young red cells by the lead; at least they are preceded by basophilia and reticulocytes and are more or less parallel to these (Aub *et al.*, 1925, review). They were described by Grawitz and Homel, 1900, and are found also in other conditions associated with anemia, but in no other disease in such numbers and in the absence of other major blood changes. They may be among the first signs of acute lead poisoning. In chronic lead poisoning they generally parallel the amount of lead exposure and the lead excretion, but not the symptoms. They are therefore a fair index of lead absorption, but not necessarily of lead poisoning. A ratio of 100 per million of erythrocytes is considered normal; 100 to 300, suggestive; 300 to 1000, diagnostic; 200, indicative of danger (J. P. Leake, 1927).

Prolonged immersion of the amphibian *Necturus* in dilute lead acetate solution leads to extensive phagocytosis of its mature erythrocytes, chiefly by mononuclear leukocytes. This appears to be connected with physical changes in the erythrocytes shown by their adherence to glass (A. B. Dawson, 1930).

The *hematoporphyrin* (protoporphyrin), which generally appears in the plasma and urine and feces fairly early in lead poisoning, is presumably formed from the destroyed erythrocytes. H. J. Kark and Meiklejohn, 1942, attribute it, and the stippling, to inhibition of hemoglobin formation. Toxic porphyria may also result from barbiturates and sulfur preparations, but lead is the most frequent cause, so that it is a valuable diagnostic criterion (Curschmann), if the urinary porphyrin exceeds 0.5 mg. per day. It tends to increase as the poisoning advances and to decrease with its improvement, but it does not parallel the symptoms. It may be high in "healthy" lead workers (Franke and Litzner, 1935; E. Roth, 1935; Carrie, 1936; K. Salomon and Cowgill, 1942).

Lead Pallor.—The color of the skin and mucous membranes is conspicuously pale and often slightly icteric in nearly all victims of lead poisoning exposed at least eight weeks. This lead complexion ("Bleikolorit") is of diagnostic value; it is too subjective to be decisive, but it should lead to the search for other signs. The pallor is greater than would correspond to the blood count, and the combs of roosters grow cold and shrink. It is usually attributed to vascular spasm, but this is improbable, since it does not vary periodically, as do the other lead spasms. It might be due to diminished blood volume, a suggestion that has not been tested.

The *blood pressure* is not affected by lead poisoning, except during the colic attacks when it rises (Riegel and Frank, 1874), largely by the compression of the intestinal vessels (Welch and Mall), partly by the pain reflex. The pulse is often slowed to 50, sometimes even to 20. In the absence of actual colic, the systolic and diastolic pressures average normal (Belknap, 1938). Pressures above 140 are rather exceptional. Chronic hypertension and arteriosclerosis do not appear to be more common in lead workers than in others (M. R. Mayers, 1927); nor can they be induced by long-continued lead administration in rabbits (Dominguez) or dogs (Adler, 1914).

Occasional attacks of spasmodic contracture of the *retinal vessels* may occur, perhaps analogous to the colic attacks, and cause temporary or permanent blindness

Constriction of excised or perfused arteries by the direct addition of lead salts (Siccardi, 1913) is an entirely different phenomenon.

Nephritis in acute and subacute lead poisoning involves direct tubular damage. In chronic clinical lead poisoning, contracted kidney develops only after long exposure, by sclerosis of the kidney vessels, followed by epithelial degeneration, deposition of calcium phosphate and finally cirrhosis (Bright, 1827).

The uric acid and nonprotein nitrogen of the blood are increased (Folin and Denis, 1913). During the colic the urine flow and chlorides are diminished; increased after the attack (Nistico, 1913); the urinary nitrogen increases during the acute attacks; the uric acid is said to be diminished during attacks (Goetze, 1892). *Intranuclear acidophile inclusion bodies* were demonstrated by S. S. Blackman, 1936, in the tubular renal epithelium and also in the liver cells, of lead poisoning, in children and in animals. Rats and dogs fed with lead for six or seven weeks develop marked hypertrophy of the kidneys and spleen, with irregularity of the tubular epithelium, intranuclear inclusion bodies and enlargement of the nuclei of many of the tubular cells (Calvery *et al.*, 1938).

Other Visceral Changes.—The long-continued administration of sublethal doses of lead carbonate to guinea pigs produced severe degenerative and necrotic change in the renal and hepatic epithelium, hemorrhagic edemas and chronic pleurisy (Ophüls, 1915). *Liver damage* is rare, although the reticular endothelium retains lead and excretes it by the bile. *Hepatic cirrhosis* may be produced in animals by lethal or slightly sublethal doses of lead (McJunkin, 1915). Von Glahn and Flinn, 1939, investigated the effect of *yeast* on the incidence of liver necrosis and cirrhosis in rabbits ingesting lead arsenate.

Gout is of fairly frequent occurrence in lead workers. The urate tophi are said to be rich in lead. There may also be periodic attacks of acute flocculatory arthritis, more or less similar to gout. *Arthralgia* occurs in about half the patients. After some preceding muscular weakness there are sudden paroxysmal attacks, generally at night, of violent remitting pains and disturbed functions of joints and groups of muscles, especially those of the shoulder and the flexors. Pressure gives some relief. The attacks last generally from five to eight days and often recur. They bear a resemblance to attacks of gout, and it is possible that they are due to a similar cause, perhaps precipitation of lead phosphate about the joints. Or they may be neuralgic, neuritic or central. *Other occasional sensory nervous phenomena* are: neuralgia, anesthesias and other hyperesthesias occurring in attacks of eight to eleven days' duration; amaurosis, amblyopia, deafness.

Intestinal colic is preceded by continued minor digestive disturbances; pressure sensation in the epigastrium; anorexia; obstipation; and some abdominal tenderness. Constipation is generally attributed to local astringent action. The acute attacks consist in paroxysms of intense pain, radiating from the umbilicus, and relieved by pressure. The patient therefore retracts the abdomen so that this often appears boat-shaped (scaphoid); he may lie on the face with the fists pressed against the painful region. The skin is pale and dry; the temperature low; the blood pressure high; the pulse hard, wiry and slowed, often to 40 or 50. The colic is sometimes accompanied by dyspnea (spasm of the bronchial muscles), and sudden severe muscular pains, especially in the flexors of the legs. After some hours the pain disappears completely, but the constipation lasts some days. Nausea and vomiting are frequent. Relapses are the rule and the whole attack may last ten days. The colic is very painful and wholly incapacitates the patient, but it is not dangerous.

Analogous effects may be produced in animals; except that with these diarrhea may be more common than obstipation. Radiography shows either increased peristalsis (producing diarrhea) or extreme tonic spasm (obstipation), so that the intestines appear like a cord (Herz; Wassermann, 1916). These effects are peripheral, since they are not prevented by section of the vagi (Harnack). They may sometimes be arrested by atropine, but this may fail clinically, and also in animals (Hanzlik). They are probably provoked by active mobilization of lead. The action appears analogous to barium and allergic stimulation, and is probably independent of the innervation. Intestinal spasm may also be produced acutely by intravenous injection of lead acetate (Hirschfelder, 1915) and in excised intestines (Siccardi, 1915), but it is questionable whether these effects are analogous.

Nervous phenomena include a variety of manifestations, some quite distinct, others more or less confused. The greater part may be reproduced in animals. They generally develop rather late, tend to spread, and are difficult to localize sharply. They involve probably direct peripheral actions on the sensory and motor elements; neuritis; and meningitis.

Wrist Drop and Other Muscular Paralyses.—Special groups of muscles, most commonly the extensors of the forearm (distribution of musculospiral below supinator longus) or others most exposed to fatigue (Mellon, 1913) become gradually paralyzed. The condition generally begins with weakness, tremors and disturbed sensation and passes through progressive paralysis, with the "reaction of degeneration" (muscles responding to galvanic and not to faradic stimulation, Eulenberg; Erb). Finally there is muscular atrophy and contracture. The contracture begins usually at the metacarpocarpal articulation of the two middle fingers, then the two outer fingers and the thumb and then the wrist. The onset is sometimes sudden. There is no pain. Restoration may occur even from advanced stages. The paralysis sometimes involves the recurrent laryngeal nerve (change of voice); and rarely the phrenic, with fatal termination. It has not been definitely decided whether the palsy is neuritic, spinal or muscular. The nerve trunks in clinical cases generally show interstitial neuritis, which is probably the primary feature (S. Moritz).

Harnack reported that methyl lead compounds affect skeletal muscle directly, rendering it more subject to fatigue. This has not been fully confirmed, and would in any case be more probably attributable to the onium structure than to the lead. Steinman, 1939, found that lead poisoning of frogs increases the hydrolysis of phosphocreatine, which would tend to prevent the development of full tension and delay recovery.

General asthenia, lassitude and neurasthenia are common. They may be early manifestations of the paralysis, or they may be merely the consequences of anemia and malnutrition. *Tremors* of the fingers, tongue, lips and eyelids are nearly always present. They may be due to weakness, or to neuritis, or early manifestations of encephalitis. *Sensory phenomena*, numbness of the hands and especially of the feet, were the chief symptoms in the slow poisoning observed by H. B. Williams, 1939.

Encephalopathia Saturnalis. — Cerebral symptoms are relatively rare. They occur especially in the rapid, severe cases, particularly with the easily absorbable tri- and tetraethyl lead; but also experimentally with hypodermic injections of lead carbonate in cats and clinically with oral administration. They are seen much more frequently in children than in adults. Negroes are said to be especially susceptible. The phenomena are the same in man and animals (Harnack, 1878; Erlenmeyer, 1913, cats; Calvery *et al.*, 1938, dogs). They set in rather suddenly after a latent period of variable duration, usually some weeks, with restlessness, hallucinations, delirium, melancholia, ataxia, pareses and pseudoparalyses, coma and epileptiform convulsions. *Children*, in the acute stage, have convulsions, with meningeal irritation and increased intracranial pressure; often with permanent sequels of convulsions and other cerebral symptoms (review, Haverfield *et al.*, 1940). All but one of twenty children who had been poisoned in infancy did not progress satisfactorily at school, and three had recurrent convulsions (R. K. Byers, 1943). Cats show significant changes in the electroencephalogram (Steinman and Therman, 1939). The prognosis is grave. The symptoms have an anatomic basis in meningitis with hemorrhagic edema and widely disseminated morphologic nerve changes, central and peripheral.

The *histologic lesions* of the nervous system in acute, subacute and chronic experimental lead poisoning involve the centers, peripheral nerves and muscles. They consist chiefly in diffuse degenerative encephalopathy without inflammatory changes. The nerve cells of the cortex and midbrain, less so in the cord, show all stages of degeneration, from acute swelling and chromatolysis to complete disintegration and liquefaction. Muscle cells exhibit fatty degeneration (A. Ferraro and Hernandez, 1932; Ewserowa, 1929; F. F. Grünberg, 1930; Erlenmeyer, 1913).

Sex functions and progeny are seriously affected by chronic lead poisoning.

Menstrual disturbances, dysmenorrhea, menorrhagia and amenorrhea are rather common. Lead always exerts an unfavorable influence upon *pregnancy*. The number of miscarriages in women affected by lead poisoning is large; of the children borne, by far the largest proportion die during the first year of life (Legge, 1901). In rabbits, lead poisoning injures the chorionic epithelium and causes coagulation necrosis and hemorrhages, with death of the fetus, which is sometimes retained for a long period (Datnow, 1928; Mitsui, 1934). Rats appear resistant to this effect; feeding of fairly large doses of lead acetate over long periods had no effect on the fertility or fecundity (H. P. Morris, 1937).

Plumbism of Father on Offspring.—The clinical evidence is slender. Sterility, stillbirth and early death of the children are common clinical occurrences. If the children survive, they are particularly liable to various nervous affections (Adami). Experimental feeding of lead acetate to male rabbits and fowl also results in smaller offspring of low vitality (Cole and Bachhuber, 1914). Weller, 1914 to 1916, confirmed this on male guinea pigs fed on lead carbonate, finding sterility or reduction of birth rate, early death of the fetus, and especially retarded development (underweight), which persists through life. In most of the lead-fed guinea pigs there are no demonstrable histological changes in the testes; a few, however, show complete aspermatogenesis, with atrophy and vacuolar degeneration of the germinal epithelium. Gradual recovery occurs if the administration of the lead is stopped, indicating that the deleterious action is confined to the maturing cells.

Lead Prognosis.—Slight, acute or subacute lead poisoning can be cured completely without any permanent disability, but the lighter grades of chronic poisoning are likely to decrease resistance indefinitely; severe grades are incurable and tend toward complete disability.

Prophylaxis.—The public, and especially the artisans, should be thoroughly educated to the insidious dangers of lead, and to guarding against the chances of poisoning. The sources of danger—lead pipes and so forth—should be eliminated. Proper precautions are essential in exposed trades and should include periodic health examinations, with especial emphasis on the lead characteristics. Lead-laden dust is especially dangerous. Since the main channel of poisoning is by the mouth, meticulous cleanliness should be enjoined and made possible by liberal facilities for washing. Sulfates are useless (see absorption). Food should not be permitted on the premises, and the clothing should be changed before leaving the works.

Ascorbic acid has no effect on the development of chronic lead poisoning or on the symptoms, in controlled experiments (Ecker *et al.*, 1940) or clinically (Dannenberg *et al.*, 1940; E. E. Evans *et al.*, 1943), nor does lead affect the utilization of ascorbic acid or complement activity. However, guinea pigs on diets deficient in ascorbic acid develop more severe nervous symptoms (paralysis and convulsions) in chronic lead poisoning; but if these symptoms have started, they are not relieved by administering ascorbic acid (Pillemer, Seifter *et al.*, 1940). *Pectin* diminishes the absorption of dietary lead (H. K. Murer and Crandall, 1942). The toxicity of lead chloride is affected by the quantity and quality of protein consumption (H. D. Baernstein and Grand, 1942).

The treatment during the active attacks consists in rest, symptomatic measures and attempts to lower the lead concentration by *deposition*. To this end, the diet should consist chiefly of milk, vegetables and potatoes; and the administration of calcium gluconate, 0.5 Gm. in milk, every three hours. All the mobilizing measures (including sodium bicarbonate) should be avoided (Aub *et al.*, 1926). The *symptomatic treatment of the colic attacks* consists in hot stupes or bath; magnesium sulfate, an ounce in half a glass of water (acting chiefly by the magnesium ion); morphine as needed. Half a pint to a pint of olive oil may be given as enema or by mouth. Amyl nitrite gives some relief (Riegel, 1878), but it is not sufficiently lasting. Atropine is ineffective. Irritant cathartics (castor oil, senna, calomel) should not be used. Slow intravenous injection of 10 cc. of 20 per cent calcium gluconate or chloride solution is reported to arrest the colic and shorten the attack (Aub *et al.*, 1926; Schretzenmayr and Baur, 1936). Thiosulfate has been suggested as antidote, but is ineffective in animals and even *in vitro* (Linguerri, 1933). In the acute lead encephalopathy of children, surgical decompression relieves the symptoms and prevents sequels (Haverfield *et al.*, 1940). *Mobilization of the lead* after and between the active attacks is advised by Aub, to hasten the removal of the depot-lead from the body. Belknap, 1935, urges that the de-leading be started before there are active symptoms. There is some risk, however, of provoking an attack (fatal, in animals; Schachnowskaja); and Kehoe, 1935, points out that the amount mobilized at the rate of 1 to 3 mg. per day in a ten day course does not make much impression on a store of 200 to 800 mg. This objection also applies to BAL (H. W. Ryder *et al.*, 1947). A diet low in calcium and high in phosphate would be safe and somewhat helpful in promoting the excretion of mobilized lead as the insoluble phosphate (Shelling, 1932; I. Gray, 1935).

The *measures commonly employed for therapeutic mobilization* are sodium bicarbonate, 20 to 30 Gm. per day; or ammonium chloride, 5 to 10 Gm., five times daily for three days; or sodium iodide (first recommended by Melsens, 1849), 0.75 Gm. per day for three days. Weyrauch, 1932, contends that lead excretion is not increased by ammonium chloride or by meat. *Sodium citrate,* 15 Gm. daily, materially increases the fecal and urinary excretion of lead, decreases its concentration in the blood and markedly improves the symptoms (S. S. Kety and Letonoff, 1943).

TETRAETHYL LEAD

The addition of this compound, $Pb(C_2H_5)_4$, increases the efficiency of gasoline motors, by preventing premature explosion (Midgeley and Boyd, 1922). It is highly toxic, being readily absorbed by the lungs and skin, and producing the phenomena of acute or subacute lead poisoning. Its combustion with gasoline results in lead chloride, bromide and sulfate, in the form of fine dust, which would therefore also be highly toxic (A. Hamilton *et al.*, 1925). Acute fatalities occurred in the manufacturing and blending, until proper precautions were taken. The danger to the public appears to be insignificant. Even attendants at filling stations dispensing large quantities of ethyl gasoline do not show any increase of lead level (Kehoe *et al.*, 1936), nor any lead symptoms (G. Lind, 1936).

Tetraethyl lead is a clear, heavy oily liquid of peculiar odor, somewhat volatile at ordinary temperature. It is practically insoluble in water, soluble in alcohol and fat solvents. The *annual consumption* in 1937 in the United States amounted to over 42 million pounds of lead, a third of a pound per capita.

Fate.—Tetraethyl lead is *absorbable* from the lungs, skin and digestive tract. Its immediate distribution in the organs presumably differs from the water-soluble compounds, but it is rapidly decomposed by the tissues and is then distributed as is water-soluble lead, and acts as such. The *excretion* occurs as inorganic compounds and may reach 8.4 mg. of lead in the daily urine (Kehoe and Thamann, 1931). It is rapidly destroyed in the body. The concentration of 11.4 mg. per Kg. of tissues is fatal (R. A. Mortensen, 1942).

Phenomena of Tetraethyl Lead Poisoning.—Application to the skin causes some irritation and local epilation (Templeton *et al.*, 1938). The systemic effects are similar to those of other lead poisoning (Kehoe, 1925). They occur usually by a combination of skin absorption and inhalation of vapor over considerable periods, but may set in after a few days if high concentrations of the vapor are inhaled, or large skin surfaces have been covered. Nervous symptoms tend to predominate. Insomnia and mental irritability and instability are among the earliest and most constant features. Other subjective symptoms are nausea, anorexia and vomiting; vertigo and headache; asthenia, and itching of the skin. The most constant objective phenomena are pallor, due to subnormal blood pressure, with subnormal temperature; loss of weight; and tremor. Relatively infrequent and unimportant are colic, lead line and stippling. The hemoglobin is usually normal. In severe acute cases the nervous irritability culminates in maniacal delirium. Such patients usually commit suicide if unrestrained, or die with cerebral symptoms. Inhalation by animals also results in acute lead poisoning (Demel *et al.*, 1933). Treatment could be attempted by calcium administration (Aub *et al*).

Experimental Poisoning by Organic Lead Compounds; Relation to Chronic Lead Poisoning.—Harnack, 1878, aimed to hasten the actions of lead by introducing it as a soluble and nonprecipitant organic compound, with the expectation that this would penetrate as such into the cells and be there decomposed, with the liberation of lead in active form. He experimented with triethyl lead acetate $(C_2H_5)_3Pb.C_2H_3O_2$. Intravenous injection caused immediate effects (which were probably due to flocculation): signs of agony; salivation and vomiting; psychic disturbances; distress and arrest of respiration. The course is rapid, so that the animal may be dead or completely recovered in a few minutes. Then, after one to several hours, phenomena gradually develop which resemble the symptoms of ordinary lead poisoning, including direct depression of striped muscle; peripheral stimulation of intestine; central motor stimulation. These differ relatively in different animals. Frogs and rabbits show mainly the muscular paralysis, whereas dogs die from the central effects before the muscles become paralyzed. Cats are intermediate. The intestinal phenomena occur with all the mammals. These delayed actions are attributed to the liberation of lead ions from the compound. This is based partly on the complete decomposition of the compound in the body, partly on the latent period, and partly on the close resemblance of the symptoms to those of chronic lead poisoning.

Triethyl lead chloride was studied by E. C. Mason, 1921, on dogs, but the identity of his preparation appears rather questionable.

THALLIUM

Thallium acetate has been used in children as a temporary depilatory in favus and ringworm of the scalp. Its therapeutic use has repeatedly caused severe poisoning and does not appear justified. The toxic phenomena resemble those of other chronic metal poisoning, but develop more rapidly, with malnutrition, epilation, polyneuritis, encephalopathy and degenerative changes in the ductless glands. It is also toxic to plants.

Historical.—Thallium was discovered by Crookes, 1861, through its characteristic green line in the spectrum. It is obtained as a by-product in the purification of cadmium and in the manufacture of sulfuric acid from iron pyrites. It is related to gallium and indium, and forms monovalent and trivalent salts; Tl_2O, thallous; Tl_2O_3, thallic. The thallous alone have been extensively studied, as the acetate and sulfate, chiefly because they are more stable. The relation of valence and action has been investigated by Iljin *et al.*, 1938. The toxic effects were shown by Lancy, 1863, and investigated by Blake and Luck, 1891, and Luck, 1895. It was tried in *syphilis* by S. Pozzi and Courtade, 1883, but was soon abandoned; later experimental studies showed it to be ineffective (Buschke, 1911, monkeys; Levaditi, 1921, rabbits). Combenale, 1898, introduced the therapeutic use of the acetate (5 to 10 mg. per day) against *night sweats.* It was effective (Buschke and Peiser, 1923), but its clinical use was abandoned because it was often followed by toxic manifestations, including temporary loss of hair. Sabouraud tried it clinically for *depilation* in 1897 and 1898, both internally and externally (1 per cent ointment, not more than 2 grains of wheat, to a limited area). He did not publish until 1912, because the results were rather unsatisfactory; the oral dosage was too low, and the thallium does not act locally (Dixon, 1927). The depilation formed the starting point of a series of studies by A. Buschke and co-workers, beginning with 1900. Successful internal use was first reported by Cicero, 1919, in a series of children with ringworm of the scalp. The clinical treatment was also developed independently by Buschke, Langer and Scheyer, 1926. The literature was reviewed by Peter, 1926, and by Buschke and Peiser, 1931.

Fate.—Thallium acetate is very soluble in water, and is readily *absorbed*, even from the skin. It reacts to form the sparingly soluble chloride, so that death is delayed even with intravenous injection (Sapiema, 1904). It is, however, *distributed* through all the organs (Dixon, 1927). In chronic poisoning its concentration is highest in the liver, brain and skeletal muscle, relatively low in the kidneys, none in the fat. It is *excreted* chiefly by the urine, beginning two and a half hours after its oral administration. In dogs, 62 per cent of the amount administered orally was excreted in the urine in thirty-six days (P. A. Shaw, 1933) in rabbits, 70 per cent in thirty days and 14 per cent in the feces (Testoni, 1933). It appears in the gastric juice of rabbits in a few minutes after hypodermic injection, but the concentration is less than in the blood; it increases materially in the intestines, owing to biliary excretion. It is somewhat reabsorbed in the digestive tract. It passes into the fetus (J. Frey and Schlechter, 1939). The milk in fatal cases may be toxic to the sucklings (K. Ehrhardt, 1927).

Etiology of Poisoning.—Thallium is more treacherous than lead and nearly as toxic as arsenic, and is used for homicide in place of the latter (Steidle, 1939). Alopecia is the only distinctive symptom, and as this takes several weeks to develop, it is absent in the acute and many subacute cases (A. O. Gettler and Weiss, 1943). Neuritis and other serious effects have been produced by a proprietary hair-removing *ointment* ("Koremlu"), containing approximately 7 per cent of thallium (reports in J.A.M.A., 1931; similar reports from Italy, Ciambellotti, 1929). Poisoning has resulted from its therapeutic use internally, especially by adults; from its employment in rat poisons, and in the industries—the latter generally chronic. More than twenty-three deaths were on record in 1931, and extensive series have been reported since then (Munch *et al.*, 1933; bibliographies, Swain and Bateman, 1910, including the older literature; Buschke and Langer, 1927). The toxicity is believed to be distinctly lower before puberty (Buschke and Markus, 1929).

Course of the Acute Poisoning.—Thallium poisoning develops slowly. With large overdoses, death occurs in twenty-four to forty hours, chiefly by hemorrhagic gastroenteritis, with terminal dyspnea (O. Gessner, 1931). Generally, the course is much slower. The group reported by Ginsburg and Nixon, 1932, involving a family of eleven, of whom six died, is illustrative. The symptoms within the first twenty-four hours consisted of tingling and pain in the hands and feet, severe paroxysms of abdominal pain and vomiting without diarrhea; then weakness of the extremities; traces of albumin and some hyaline casts in the urine; marked stomatitis and salivation, some with a "lead line"; blebs forming on lips. Within two to five days, all developed encephalopathy with cranial nerve palsies, disturbed sensorium, myoclonic movements of the extremities and head. The more toxic patients passed into convulsions, then marked delirium, coma, and death by respiratory failure. The temperature rose to 103° F. within twenty-four to forty-eight hours before death, with signs of pulmonary edema and bronchopneumonia.

With continued administration of smaller toxic doses, the symptoms ordinarily become perceptible in about a week and reach their acme by the end of the second or third week, and in favorable cases begin to retrogress about four weeks later. If the dosage was not too large, or too long continued, the recovery may be complete. In fatal cases, death generally occurs after several weeks, with severe nervous symptoms and gradual decline (Heinichen, 1931). The *phenomena of the slow poisoning* include stomatitis and hemorrhagic gastroenteritis, with diarrhea, but without the spastic constipation of lead poisoning; loss of hair and dermatographia; marked hyperexcitability of the sympathetic system; peripheral neuritis, pain in the extremities, tremors of the hands, weakness of the muscles; sometimes optic atrophy; glomerular nephritis, with polyuria and persistent albuminuria; inhibition of growth and sexual development, with degenerative changes in the endocrine glands, thyroid, parathyroid, gonads and suprarenal, and of other viscera; alterations in basal metabolism, blood sugar level and calcium; rickets and gray cataract; swelling of the reticulo-endothelial cells of the liver and spleen; restlessness, obstinate insomnia, depression, dementia and other neuroses, with degenerations in the basal ganglia, optic nerve and cerebellum.

The **treatment** in acute cases would consist in gastric lavage. Various antidotes have been proposed, such as iodide, thiosulfate, pilocarpine, calcium salts (Munch, 1934), but their value has not been demonstrated and their rationale appears doubtful.

Clinical Depilation.—Thallium acetate is, or was, used only in children younger than ten years, in a single dose of 8 mg. per Kg. of body weight, exactly measured, by mouth, generally in water. The hair becomes brittle in about a week and comes out more or less completely for the following two weeks, generally with some minor toxic manifestations. It is restored in about six weeks, perhaps even more abundantly than before. If the dosage is too large, the alopecia may be permanent. Biopsies show distinct lesions in the hair bulb and sheath, with later regeneration, but some of the follicles undergo sclerosis (Traffi, 1928).

Experimental studies of the depilation have been made especially in rats and confirmed on other animals (Buschke, 1911). The susceptibility varies in different individuals. It may be obtained with a single dose of 14 to 18 mg. per Kg. (Cooper and Engmann, 1931), or daily doses of 0.5 mg. per Kg., of thallium acetate (Buschke and Peiser, 1926), by mouth or hypodermically, or local application of 0.1 to 1 per cent ointment. The phenomena correspond exactly to those of the clinic, in kind and in time (Buschke and Peiser, 1926). Smaller doses may stimulate the growth of hair (Dixon, 1927; Cooper and Engmann, 1931, a single dose of 5 mg. per Kg.). *Histologically*, the depilation stage shows the hairs split and broken, the hair follicles often enlarged, changes in the keratinization of the epithelium and scaling (F. Hecke, 1928; Buschke and von Vasarhelyi, 1932). The perifollicular nerves show degeneration (Cortella, 1933). Petechiae and eruptions are sometimes seen clinically (Prokoptchouk *et al.*, 1930). The suppression of sweating is probably due to these skin changes. The depilation includes all the body hair, which is innervated by the sympathetic; while the sensory hairs, which have a cerebrospinal innervation, escape. On this basis, Buschke and Peiser, 1926, attributed the depilation to sympathetic stimulation, and Dixon, 1927, described increased excitability of sympathetic nerves to electric stimulation; but H. C. Chang, 1931, showed that the alopecia involves also denervated autotransplants. The change of susceptibility with age might suggest an endocrine action; for instance, administration to lactating rabbits may cause alopecia of the suckling without affecting the mother (Vasarhelyi, 1928); but excision of the thyroids and ovaries has no effect in either direction (Chang, 1931).

Internal Organs.—Thallium produces destructive changes, especially in the sexual glands, but also in other endocrine glands, in the lymphatic system and in the other viscera. The gastro-enteritis has been mentioned. These all progress and retrogress coincident with the general course of the poisoning and of the depilation. The most marked changes are in the spermatogenesis; namely, disintegration of the spermatic cells, azoospermia, suppression of mating. Corresponding suspension of *estrous cycle* is observed in mice (Buschke and Markus, 1929), but not in rats (A. J. Cox and Rodgerson, 1935). The *adrenal cortex* shows marked vacuolization (Hecke, 1928); Buschke and Markus, 1929, and Koyanagi, 1930, connect this with increase of the *blood cholesterol*, which occurs at the same time. The *thyroid* also shows changes, which may be connected with a decrease of the *basal metabolism*, described by Mu and Hu, 1930. The blood sugar level rises during the first ten days, then falls below the normal (Mamoli, 1926); with intravenous injection, hypoglycemia precedes the hyperglycemia (Koyanagi, 1930). The serum calcium is lowered, with softening of the bones and rachitic changes in prolonged poisoning (Buschke and Markus, 1929; Koyanagi, 1930). These suggested parathyroid deficiency (Buschke and Markus), but Mamoli, 1926, did not find any changes in this gland; he was inclined to attribute the *cataract*, which may also occur, to the hyperglycemia. Young rats regularly develop cataract in both eyes, differing from other toxic cataracts, naphthalene, diabetic and tetany (Donski, 1932). The *blood picture* shows leukocytosis and erythropenia, with normoblasts (Mamoli, 1926), but no stippling (Testoni, 1930; Viola, 1933). Pathologic changes in the lymph nodes and thymus, liver, pancreas, lungs and kidneys were described by Hecke, 1928, and Prokoptchouk *et al.*, 1930.

The *histopathology of the central nervous system* was described for a human case and for apes by E. Scharrer, 1933. The changes involved the olivary and dentate nucleus and Goll's columns and the anterior and posterior horns of the cord, and are similar to those of lead. Rats and cats show marked degenerative changes in the cells of the central nervous system, in the myelin sheath, axis cylinder, neuroglia and neurofibrillary reticulum, and degeneration of the peripheral nerves (Cortella, 1930, 1931, 1933; Delfini, 1934).

Vegetation.—Thallium prevents the germination of seedlings (Dilling, 1926). Ground on which thallium sulfate is sprinkled will not bear vegetation for years (S. C. Brooks, 1932). The amount which adheres to thallium-poisoned grain, however, is not injurious to the soil (Horn *et al.*, 1934).

Antiseptic Action.—Thallium salts are somewhat antiseptic, but only in the presence of air (Buschke and Jacobson, 1922; Buschke, Jacobson and Klopstock, 1925).

APPENDIX-BIBLIOGRAPHY OF PAPERS APPEARING SINCE JANUARY 1926*

Names of Authors.—If there are more than three authors of a given paper, only the first two names are listed and the others are indicated by *et al.* The names of the other authors are listed only if they are necessary for subsequent clarity of arrangement.

In general, if an author has more than two initials, only the first two of these are given.

Articles and Books.—Under a given author the subjects are arranged alphabetically; when reference is made to several papers on the same subject by the same author, the references are arranged under the subject according to year.

Full titles of papers are not recorded; the bibliography title indicates the material in the paper significant from the standpoint of pharmacology. Thus the bibliography title is not necessarily found in the author's title.

The abbreviation *Diss.* indicates *Dissertation.*

Journal Abbreviations.—The abbreviations used in this bibliography are, for the most part, those used in the Second, Series of the *Index Catalogue of the Library of the Surgeon-General's Office, U.S. Army,* Washington, D.C., and in the *Quarterly Cumulative Index Medicus,* American Medical Association, Chicago.

Because of the numerous references to the *Journal of the American Medical Association* and to the *Journal of Pharmacology and Experimental Therapeutics,* these are abbreviated respectively *J.A.M.A.* and *J.P.E.T.*

Abstracts, References, and Proceedings.—In all abstract references, such as those of the *Chemical Abstracts* and the *Biological Abstracts,* the page on which the abstract appears is recorded rather than the code number.

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